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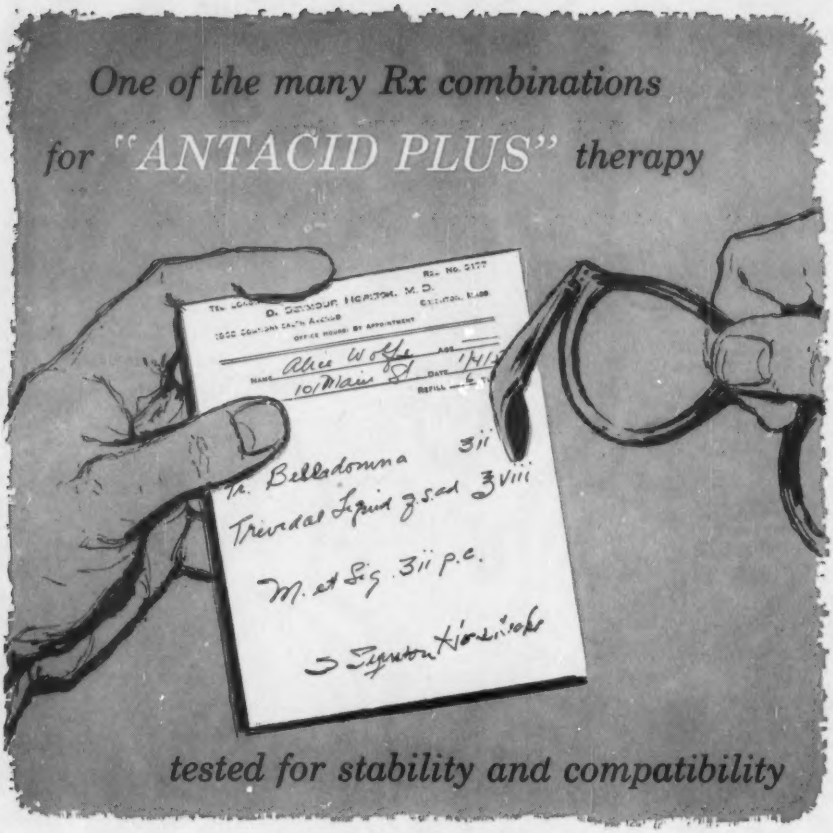

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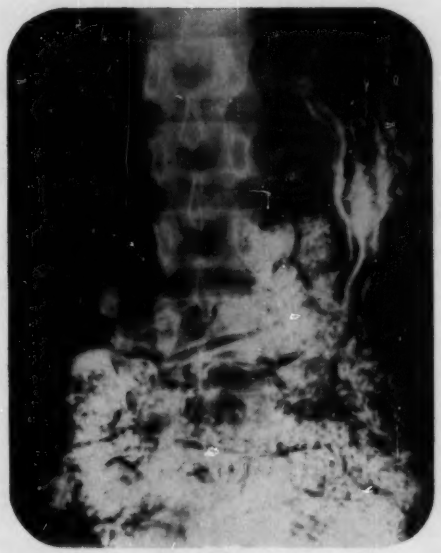
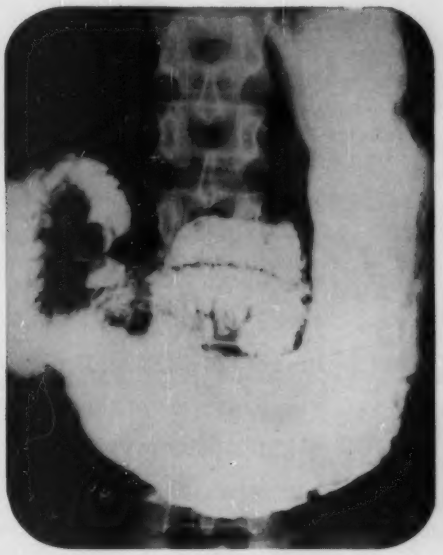


*Posterior-anterior film: definite hyperperistalsis with poor duodenal visualization.**



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The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

contents:

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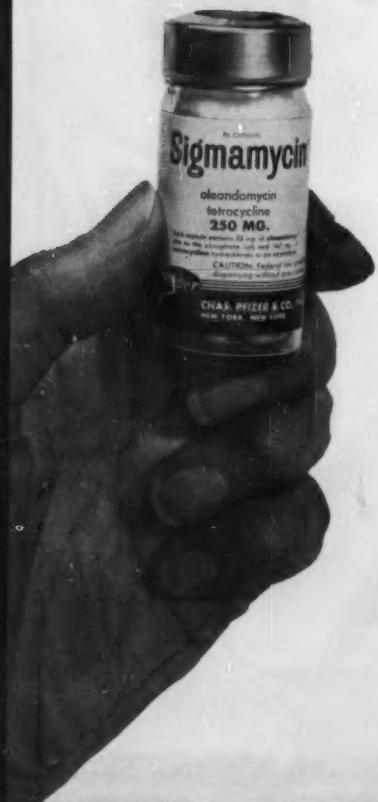

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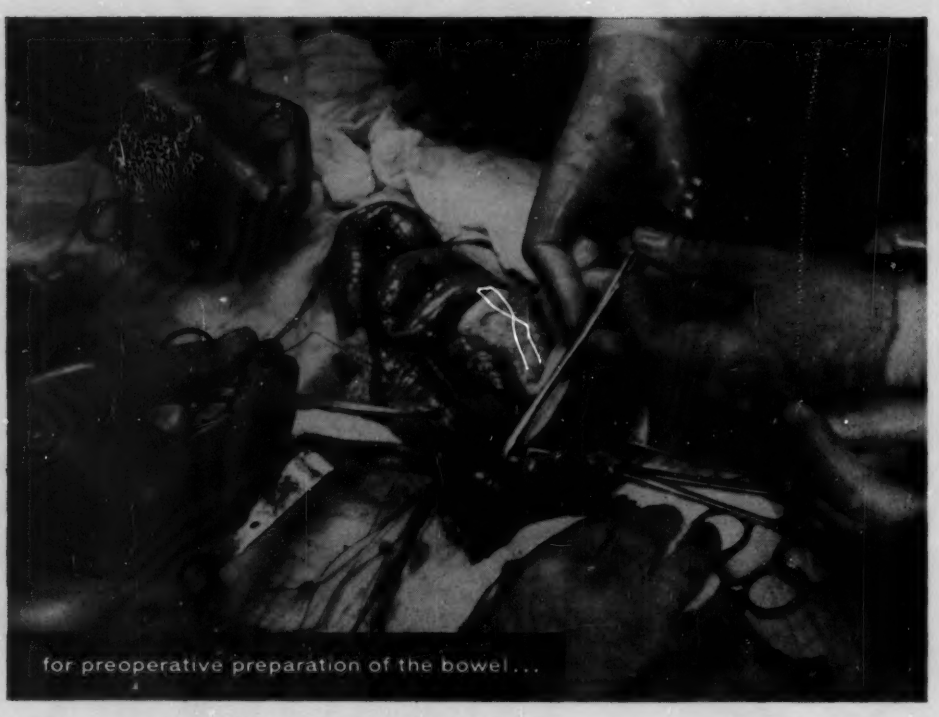

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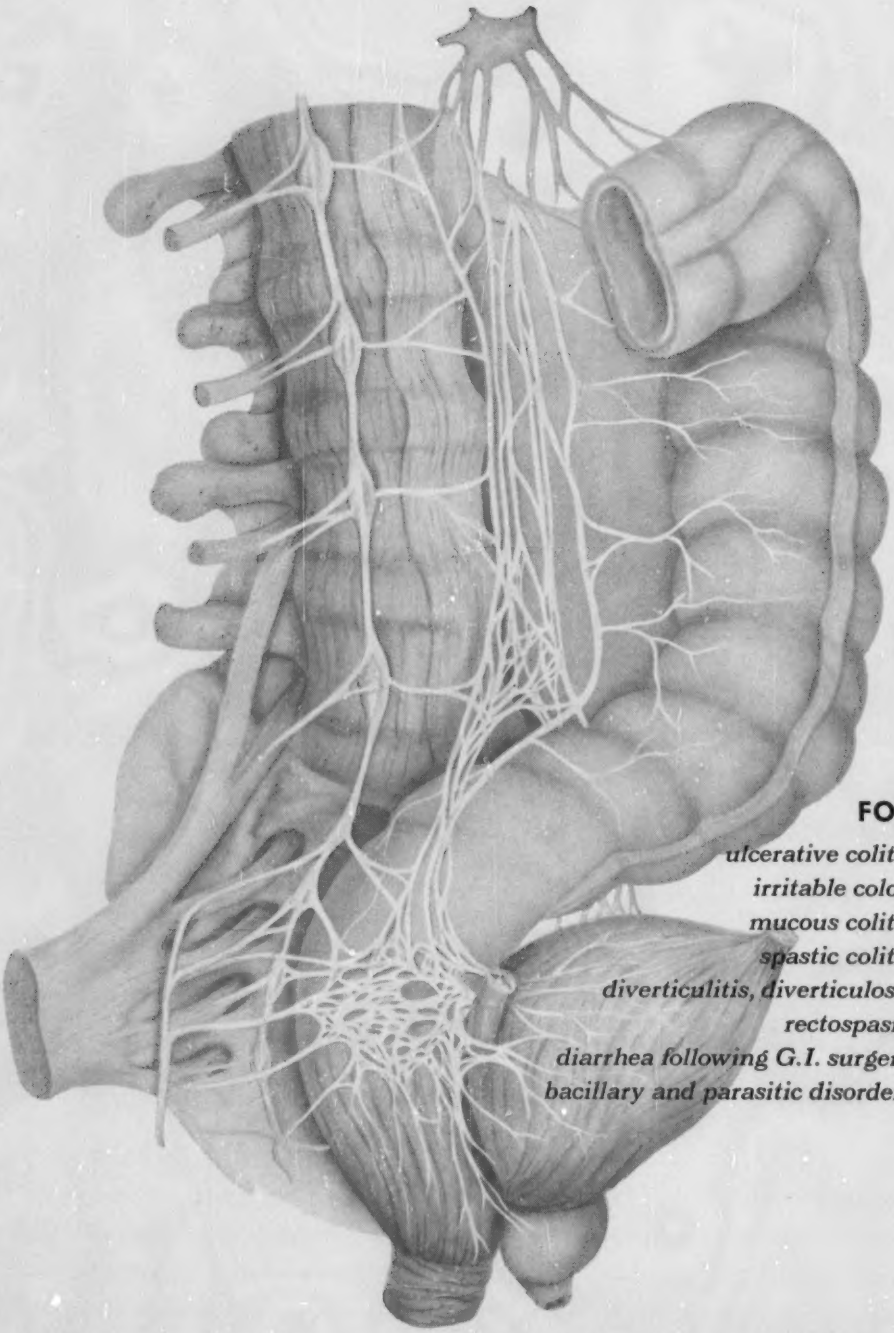

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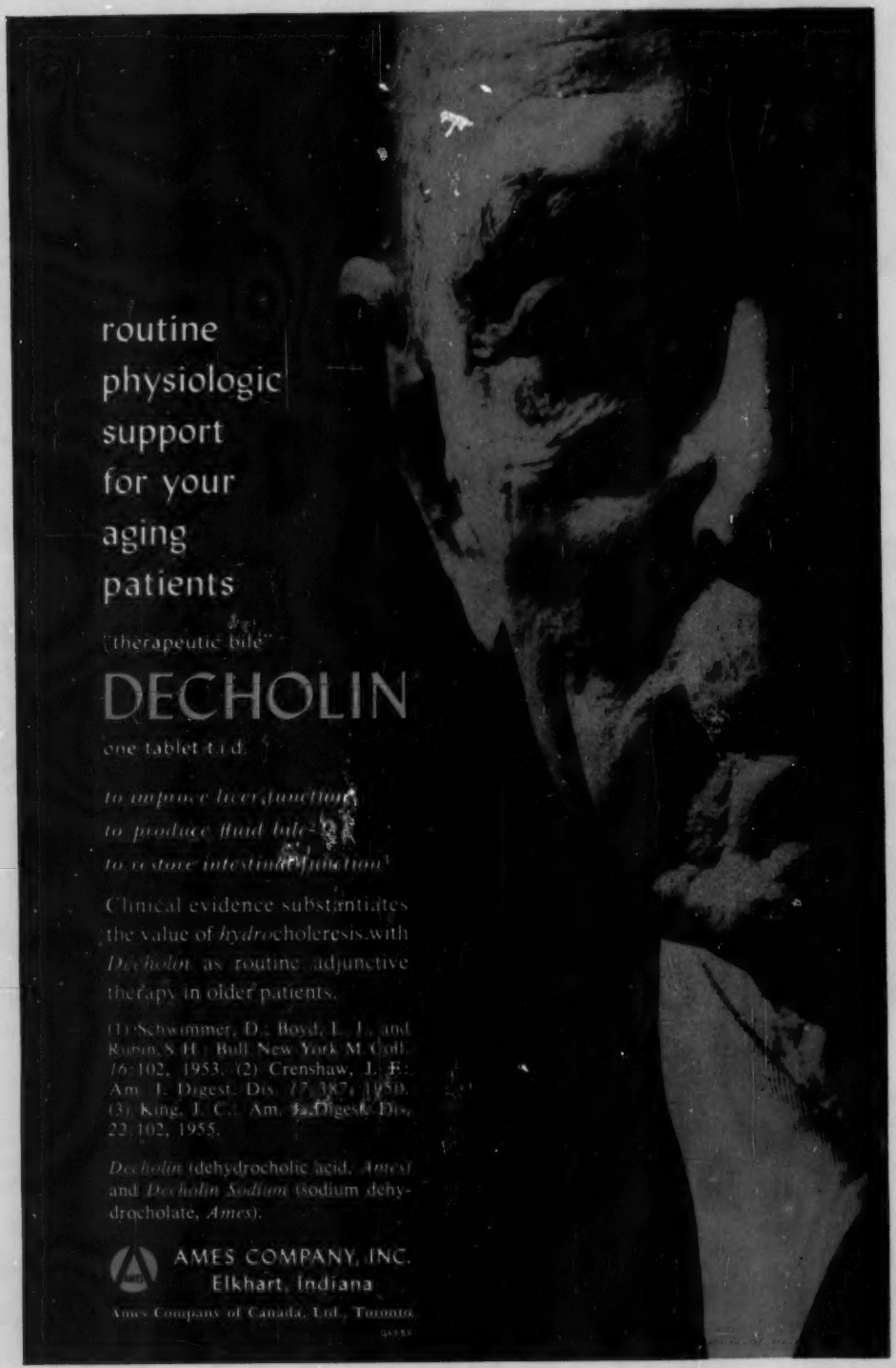
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(1) Schwimmer, D., Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. 16:102, 1953. (2) Crenshaw, J. E.: Am. J. Digest. Dis. 17:387, 1950. (3) King, J. C.: Am. J. Digest. Dis. 22:102, 1955.
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THE American Journal OF Gastroenterology

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VOLUME 27 JANUARY, 1957 NUMBER 1

EFFECTIVE INHALATION ANALGESIA IN GASTROSCOPY*

MILTON J. MATZNER, M.D., F.A.C.G.†
STANLEY STARK, M.D., F.A.C.G.‡
and
IRVING M. PALLIN, M.D., F.A.C.An.§
Brooklyn, N. Y.

Gastroscopy, since the advent of the flexible gastroscope, has become established as an excellent safe diagnostic procedure. Recently, with the advent of the flexible obturator esophagoscope, this too has been added to the armentarium of the gastroenterological endoscopist.

The major drawbacks have been unsafe, inadequate or overly complicated anesthesia or analgesia necessary in performing these examinations. Relaxation and cooperation of the patient are essential requirements. Good psychological preparation of the patient is an important preliminary measure to endoscopy. Gastroscopy, however, has not infrequently been a very disagreeable experience for the patient, and adequate cooperation and relaxation for a thorough examination has not always been obtained by conventional means of anesthesia.

A review of the various methods of anesthesia and analgesia now in use reveal the following:–

1. Local anesthesia with Pontocaine, Pyribenzamine, cocaine or Benadryl usually combined with sedation, narcotics, or both.

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*Read before the Third Annual Convention of the American College of Gastroenterology, New York, N. Y., 15, 16, 17 October 1956.

†Attending Gastroenterologist at Jewish Hospital of Brooklyn; attending Brooklyn State Hospital and Jewish Chronic Disease Hospital; Lecturer in Medicine at State University College of Medicine.

‡Physician-in-charge Gastroenterology Department, Beth El Hospital; Gastroscopist at Brooklyn Hebrew Home for the Aged; Associate at Kings County Hospital; Department of Gastroenterology at Jewish Chronic Disease Hospital.

§Director of Anesthesia at Jewish Hospital of Brooklyn; Consultant in Anesthesia Veterans Administration Hospital, Brooklyn.

2. Intravenous meperidine hydrochloride without local anesthesia.

3. Combinations of narcotics such as Nisentil, Nalline and Scopolamine.

4. General anesthesia[1,2] (usually intravenous barbiturates) combined with local anesthesia and muscle relaxants such as succinylcholine and endotracheal intubation.

5. No anesthesia.

The various disadvantages of these combinations are obvious. We have tried them all with fairly good results but they all have certain idiosyncrasies of sufficient degree to seek other methods.

There are three major disadvantages to the local anesthetics. Two of these are the well known immediate anaphylactic type with death and the delayed type with convulsions and frequent death. The third disadvantage is not readily apparent. In the more nervous individual whose mentalization or language limitations set up a barrier to full comprehension of the objectives of the anesthesia, there is a frequent tendency towards hysteria due to the sudden inability to swallow and the sensation of inability to breathe. As a result of this, some patients have refused any instrumentation.

In 1953, Cimoch and Wirts[3] described the use of intravenous meperidine hydrochloride prior to gastroscopy, without the need of the local use of anesthesia. We immediately decided to utilize this procedure and were impressed with its effectiveness in producing both euphoria and relaxation while the patient remained awake and fairly cooperative. Disadvantages, however, immediately became apparent. A large percentage of patients had marked suppression of respiration with apparent cyanosis. The subsequent long recovery period required a special recovery room with nursing supervision before the patient could leave the office or clinic if done on an out-patient basis. Approximately 10 per cent of the patients were given Nalline to combat the respiratory embarrassment. In view of this, we soon abandoned meperidine intravenously and switched to an intramuscular combination of Scopolamine, Nalline and Nisentil. This mixture combated the tendency towards cyanosis and respiratory depression but left a lot to be desired in the way of relaxation. It, too, required a long recovery period and it was noted that patients exhibited excitement almost to delirium on occasion under the influence of the Scopolamine.

We have made no attempt to use general anesthesia with muscle relaxants and local anesthetic combinations. It was our feeling that esophagogastroscopy was a procedure that should be simplified rather than made more complex. We could not, therefore, logically add the expense of hospitalization, operating room facilities and an anesthetist to perform a simple diagnostic procedure and expect it to be universally accepted by our colleagues.

We have gastroscoped patients, especially the elderly debilitated ones, without any need of anesthesia. The resultant psychic trauma and discomfort,

however, accentuated the need of some anesthetic agent. I am sure that none of us consider endoscopy without analgesia as an adequate routine procedure. This is readily envisioned when we recall that even the passage of a Levin tube is disagreeable to many patients.

In view of the above considerations, when the effects of trichlorethylene became apparent in the fields of obstetrics[4,5], minor surgery[6], gynecology and urology, one of us (M.J.M.) suggested its use in gastroscopies. To this, we soon added its use in esophagoscopies.

Trichlorethylene (Trilene) has a wide margin of safety in an open system. It is a clear colorless, volatile liquid with a boiling point of 87°C., making it somewhat less volatile than ether. It readily decomposes on exposure to heat, sunlight and alkalis, so that cool, dark storage is mandatory. Heat causes it to break down to phosgene and other irritants, and alkali converts it[6-9] to dichloracetylene, a CNS neurotoxic substance. Respirations are never depressed in light stages, but when its inhalation is *forced* beyond the first plane of anesthesia, tachypnea, tachycardia and arrythmias develop. Tachynea is the first to appear, and therefore the first danger sign to anticipate. Trilene must never be used in a closed circuit absorption system because it reacts with soda lime as noted above. This may cause cranial nerve palsies and encephalopathy followed in some instances by death.

The advantages of Trilene appear to transcend most of the objections that we have had to previous methods. They are:—

1. No complicated apparatus or help is needed. The Duke University Inhaler is relatively inexpensive.

2. It can be used anywhere, at anytime, whether it be operating room, clinic or office without the necessity of prior heavy sedation.

3. Elimination of local anesthetics is a time-saver and avoids their inherent dangers.

4. The patient remains awake and cooperative. He controls the anesthesia so that overdosage does not occur. In the rare instance where consciousness is lost, it is only a matter of seconds before it is regained[6,10].

5. There is no limitation on working time.

6. The Trilene may be given before either Ewald or Levin tube intubation and more given as needed when endoscopic intubation is commenced.

7. Age is no factor.

8. The patients respirations are not depressed and he receives adequate oxygen through the inhaler.

9. We have found the cricopharyngeus to be more relaxed than by any previous method used and no cardiospasm preventing successful intubation has occurred so far.

10. Trilene does not cause excessive salivation or secretion of mucous[6,10-12] so that only small amounts of atropine by preliminary injection are required.

11. There is no excitement, nausea or vomiting[13].

12. Experimental studies reveal no evidence of renal or liver damage after prolonged administration[14-16]. This is important where patients having liver cirrhosis and possible esophageal varices are to be esophagoscoped.

13. Within 10 to 15 minutes after termination of the procedure, the patient may eat, drink, and go home unattended because there are no after-effects, either general or local.

The contraindications and disadvantages of trilene are:—

1. It is not recommended in patients with severe cardiac failure, or active cardiac disease[17,18] and should never be used at the same time with epinephrine, although other vasoconstrictors may be used.

2. The odor may be slightly objectionable to some patients but we have found that by starting with a minimal concentration and gradually increasing it, that the patient readily gets used to the odor.

Method:—There are two recommended methods of administration. The first is the open drop method and the second is the nonre-breathing semiclosed technic. The inhaler used by us is built for self-administration depending upon the patient's ability to maintain the anesthesia until his arm drops thereby removing the analgesic agent as unconsciousness is approached. The Duke or Cyprane Inhaler was used exclusively in this study. This inhaler provides vaporized Trilene with inhalation, but exhalation gases are expelled into the atmosphere. Thus there is no re-breathing, and therefore low resistance to gas flow without carbon dioxide accumulation. It has an attachment for supplemental oxygen, and nitrous oxide or other gases, although we never used this. This inhaler is essentially a small chromium cylinder attached at right angles to a rubber mask. The cylinder contains selfclosing inspiratory and expiratory valves, a compartment for Trilene and attached to it a chain and small strap for attachment to the patient's right wrist. One wall of the Trilene compartment is perforated and has an adjustable valve for admitting varying amounts of air on inspiration which controls the concentration of the inhaled mixture.

With the patient lying in the left lateral decubitus position to avoid subsequent positioning of the patient, and after preliminary atropine by injection, the inhaler is strapped to the right wrist. Fifteen cubic centimeters of Trilene has previously been placed within the inhaler. The valve is adjusted to minimum

concentration and the patient starts inhaling gradually. The valve is slowly adjusted to full concentration. The patient is watched for signs of tachypnea, change in color, tachycardia or arrythmia[15,19,20]. When the patient drops the mask or his jaw becomes very relaxed, he is ready for intubation (an average time of about five minutes). Endoscopy then proceeds after preliminary gastric emptying, if necessary. In the latter instance the patient is allowed to breathe additional Trilene before endoscopy. The patient holding the mask in his right hand may place it over his face at anytime during endoscopy and take more analgesia if he wishes. We have found this necessary only when endoscopy is unusually long, as for demonstration purposes.

Following withdrawal of the endoscope, the patient is allowed to rest for a variable period up to 30 minutes, although frequently only five minutes is necessary, and then allowed complete activity to the extent of taking public transportation alone in returning home. He is allowed to eat and drink as soon as he desires.

Results:—To date, we have examined 116 cases of which 91 were gastroscopies, 20 esophagoscopies, and 5 combined esophagogastroscopies.

There has been only 1 failure of intubation, and 1 failure to maintain intubation long enough for satisfactory examination.

Schindler[21] states that he has found it impossible to intubate approximately 2 per cent of patients by any method, so that the procedure in our hands presents a favorable result. The cases in which failure occurred were of the following type.

1. Patient could be intubated but because of uncooperativeness, it was necessary to remove the gastroscope.

2. Patient could not be intubated because of severe cervical arthritis.

Summary and Conclusions:—Gastroscopic examinations are at times incomplete, unsatisfactory, dangerous or unduly complicated because of the inherent discomfort of the procedure, and the inherent limitations of the previously used anesthetic agents. Most gastroscopists employ some type of preliminary sedation followed by a varied list of local and general anesthetic agents. Topical applications of pontocaine, gargling with pontocaine or cocaine solutions are supplementary procedures in common usage. More recently intravenous meperidine hydrochloride has been employed. General anesthesia with intravenous pentothal has also been used on more infrequent occasions. In our experience, these methods of anesthesia have not been uniformly satisfactory for esophagogastroscopic examination.

In an attempt to reduce the patients' discomfort by more effective anesthesia during gastroenterological endoscopy, we have employed inhalation analgesia with trichlorethylene. The degree of relaxation and decrease in the

patients' discomfort has been so marked in most instances, that we feel this should result in wider use of this valuable diagnostic procedure, in indicated cases. We do not claim that all the inherent discomfort of this procedure is removed since this would require much deeper anesthesia.

Trilene inhalation has now become our routine method of analgesia for gastroscopy and esophagoscopy in both ambulatory, private and clinic patients, as well as for hospital patients providing there are no contraindications. To date, this type of analgesia has proved most satisfactory to both patient and physician, and we hope that other endoscopists will report upon its further trial. A general good result would make this procedure even more acceptable in clinical practice.

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DISCUSSION

Dr. Jerome Weiss (New York, N. Y.):—Dr. Matzner has presented an interesting paper on the use of inhalation analgesia in gastroscopy.

We who do endoscopy, and particularly gastroscopy, are continuously striving to find more effective means and methods of conducting our investigations, and naturally, at the same time, making it easier on the person most directly involved, the patient. That we have succeeded somewhat in simplifying our methods, improving our technic, and increasing our reliability, is evidenced by the almost universal acceptance, especially of gastroscopy, as a valuable adjunct in diagnostic medicine.

It was not such a long time ago, when I was being taught gastroscopy, that our colleagues, especially the surgeons, would say that they would rather have

their patients operated on than subjected to the tortures of gastroscopy. Today we are very often called in on consultation by these very surgeons to help determine whether surgery should be done. Therefore it behooves us, as Dr. Matzner pointed out, continuously to simplify the procedure of esophagastroscopy, rather than to make it more complex, and perhaps the use of Trilene is a step in the right direction.

I should, however, like to point out our results in over some 850 gastroscopies which we had tabulated during a recent study. Using seconal one hour before, atropine by injection 15 minutes before, and 2 per cent pontocaine by swab and spray tube, we have successfully gastroscoped all but about 2 per cent of our patients, the same as Schindler and Palmer, and similar to Dr. Matzner's results, in an age group varying from 18 to 80 years old. Only one of these patients was suspected of having any reaction to pontocaine, and that was evidenced by a noticeable dyspepsia, but without convulsions or loss of consciousness.

Our anesthetists have assured us that with adequate barbiturate preparation, there should be little or no fear of reaction to the pontocaine, and so far we have found that 1½ grains of seconal seems quite adequate for our purpose. The seconal does not depress the patients to such extent as to put them completely to sleep, but does put them into a sort of hypnotic state, where they are under the will of the endoscopist, who can usually get them to swallow on command, in order to facilitate the procedure.

In varying our method, constantly looking for a more ideal one, we have found that where the patient is alert enough to swallow when requested to do so, thereby closing off the trachea, instrumentation for the most part is simple, and, of course, the danger of perforation or doing an inadvertent bronchoscopy is lessened.

Let me digress a moment to make a point that no matter what the type of premedication used in preparing the patient for gastroscopy, "vocal anesthesia is as important as local anesthesia". By this is meant that the psychic trauma accompanying this procedure is minimized if the patient is apprised of what to expect with each step of the preparation and of the instrumentation itself. We have found that a soothing voice offering encouragement has done more to simplify gastroscopy than large amounts of analgesics. It not only makes the passage easier but also later recollection of the experience is more pleasant.

One disadvantage of the use of Trilene is the apprehension most patients exhibit to any form of anesthetic mask, which probably conjures up visions of unpleasant past experience involving tonsils or appendix, and makes them feel that they are about to undergo a major procedure, which in reality they are not.

As I see it, the great advantages to be derived from this method of analgesia are the rapidity with which intubation may be commenced. This is within

an average of five minutes after beginning analgesia, as compared to an average of 20 minutes required for good local preparation to be effective. The fact that five or ten minutes after endoscopy, the patient is capable of complete activity, including eating and drinking, rather than being required to wait an hour or more for the effects of the other methods to wear off before he is able to navigate by himself is also advantageous, as is the absence of a severe hangover.

These two factors are big steps in simplifying esophagastroscopy both for the patient and the observer, and this method should certainly be utilized more frequently now as another progressive movement and as an easier and more rapid diagnostic medical aid.

PRECIPITATING FACTORS IN THE DEVELOPMENT OF HEPATIC COMA INCLUDING PRELIMINARY OBSERVATIONS OF SERUM AMMONIUM LEVELS*

A. I. FRIEDMAN, M.D., F.A.C.G.†

Hackensack, N. J.

The onset of hepatic coma is usually heralded by a prodromal period of mental confusion, delirium, disorientation and personality changes that finally yield to convulsive movements of the extremities, characteristic tremor and unconsciousness. In a patient with severe liver disease these mental phenomena, tremor and *fetor hepaticus* followed by unconsciousness are diagnostic. The EEG findings will often substantiate the diagnosis.

The 20 cases in this series of hepatic coma comprised 14 males and 6 females. The average age was 56 and ranged from 30 to 81 years. The 20 patients presented 28 episodes of coma. Coma was progressive in all but 3 patients where it was intermittent; one patient presented 4 episodes of coma over a 4-day period. The duration of coma lasted 1-5 days. There was only 1 survival in the entire series.

The diagnosis of liver disease in this group was confirmed by liver biopsy or necropsy in 17 of the 20 patients. The diagnosis was portal cirrhosis in 13, fatty metamorphosis in 3, primary hepatoma associated with portal cirrhosis in 2, hypertrophic biliary cirrhosis in 1 and in 1 patient metastatic carcinoma of the liver from the gastrointestinal tract. In the last patient we excluded the possibility that metastatic lesions of the brain could have induced the neurologic findings. Electroencephalography was done in 3 patients; in 1 the typical slow delta waves were present and in 2, the findings were normal. In a study of 180 patients with liver disease there were no consistent clinical or laboratory findings that could predetermine which patients would develop coma; nor were there any characteristic laboratory findings in patients in coma.

The precipitating factors in the development of coma in these 20 cases were: hemorrhage in 5, hemorrhage plus ammonium chloride in 2, infection in 5, infection plus ammonium chloride in 1, narcotics or sedatives in 2, protein hydrolysate intravenously in 1, methionine in 1, paracentesis in 1, ammonium chloride in 1 and diamox plus ammonium chloride in 1.

In those patients in whom hemorrhage was a precipitating factor there was no evidence of shock. The blood pressure and pulse were maintained at the normal or slightly above the normal figures. Hemorrhage was noted clinically as hematemesis or melena. In 2 patients with hemorrhage, ammonium chloride

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had been administered 3 and 5 days previously because of ascites. We have, therefore, included ammonium chloride among the precipitating factors in these cases because it may have been an adjunct in the development of coma. The only patient in this entire series who survived was a 30-year old male who entered the hospital with ascites, jaundice and fever. The fever quickly subsided but characteristic tremor, mental confusion and coma began following a moderate hematemesis. An infusion of glucose resulted in the rapid disappearance of coma. His recovery continued and he was discharged without further incident. Since no blood sugar figures were available we cannot state whether or not this patient belongs in that small group whose symptoms apparently develop because of hypoglycemia. It is interesting to review the liver profile on admission, in this patient. Total protein was 5.4 gm. with albumin and globulin evenly divided, serum bilirubin 13.8 mg., alkaline phosphatase 8.3 BU and cephalin flocculation 2 plus. There were no evidences of esophagogastric varices. The age of this patient, the youngest in the series may have been an important factor in his recovery.

The group of patients with infection presented bronchopneumonia in 3, peritonitis in 1, a perinephritis abscess in 1 and a diarrheal disease (viral?) in 1. The patient who developed peritonitis did so 3 days following paracentesis. His coma was gradual and progressive. Antibiotics were of no benefit. The organism cultured was a staph aureus. The patient with diarrhea ran a temperature of 101°-102° for 10 days but no organisms were found in the stools. One patient with a perinephritic abscess presented a bulging in the right flank for approximately 3 weeks during which time her condition gradually deteriorated. Because of marked ascites she was given ammonium chloride 2 gm. t.i.d. The CO_2 combining power dropped to 13 mEq. after 2 days of therapy and 6th molar sodium lactate was administered; the CO_2 combining power rose to 20 mEq. but quickly dropped again. During this interval mental disorientation and tremor developed. Jaundice deepened and irreversible coma supervened. Surgery without anesthesia was performed by a simple incision and drainage. Unfortunately, the perinephritic abscess was unrecognized as such, although it appeared that a simple aspiration of the mass was indicated and would have substantiated the diagnosis. It was our impression that the ammonium chloride was a factor in the cause of death.

In 2 patients the precipitating factors appeared to be narcotics and sedatives. One patient was given paraldehyde, 3 doses at 4 hr. intervals, a total of 15 c.c. for restlessness and mental confusion. He was obviously in impending coma at this time but it was not recognized as such. His condition was due to a severe fatty metamorphosis of the liver as we discovered at necropsy. For a period of 24 hrs. the odor of paraldehyde was strong on his breath. Later this gave way to *fetor hepaticus*. Coma that began 2 hrs. following the last dose of paraldehyde was progressive and fatal 58 hrs. later. We assume that paraldehyde was the precipitating factor in the development of coma. One can argue

that hepatic coma was impending and, therefore, this patient would have progressed to coma regardless of the paraldehyde. But unless one disregards all previous observations and reports[2,3] this was an instance when a sedative threw the patient into irreversible coma. In one other patient 2 doses of morphine of 150 mg. each at 6 hr. intervals were responsible for the development of hepatic coma.

The present emphasis on nervous system disturbances following the administration of a high protein diet in patients with severe liver disease relates particularly to those patients who present collateral or surgical shunts[4,5]. Up to 6 months ago such a diet was automatically prescribed in our hospital when a diagnosis of portal cirrhosis was made. No specific quantitative measure of protein intake, however, was recorded usually, and therefore, the ingestion of protein as a precipitating factor in this series cannot be properly evaluated. In one patient methionine appeared to be the precipitating factor. This was considered extremely unusual by us until we noted some of the observations reported by Dr. Sherlock and her group on the significant mental disorientation following methionine, in those patients who present collateral or surgical shunts[5]. In another patient with severe liver disease coma developed approximately 30 minutes after the intravenous administration of a protein hydrolysate (Amigen). The patient recovered from this episode 3 hrs. later then slipped back into coma for a period of 22 hrs., was in and out of coma on 3 separate occasions and eventually died. Although protein hydrolysates, like Amigen have been considered harmless in so far as coma is concerned, the time relationship in this patient appeared to be more than coincidental[2]. Perhaps in the presence of prominent collaterals intravenous protein might induce coma.

In one patient ammonium chloride alone appeared to precipitate the development of coma. Following a second dose of 4 gm. there appeared considerable mental confusion and coma. The cessation of ammonium chloride after 3 doses was followed by a remission that lasted 2 days but coma recurred with a fatal termination. Diamox (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide) has been condemned in the treatment of severe liver disease because the electrolytic disturbances provoked by the inhibition of carbonic anhydrase results in a depression of cerebral metabolism. In one patient the administration of ammonium chloride and Diamox in an attempt to remove ascites was followed by the development of coma. This patient, a 57-year old male with ascites and jaundice was admitted following a moderate epistaxis which ceased shortly following admission. On physical examination he presented spiders in great profusion, a beefy tongue, marked ascites and a liver 4 finger-breadths below the costal margin. Hemoglobin was 9.6 gm.; R.B.C., 2.8 million; W.B.C., 4,600 with 70 per cent polys; serum bilirubin, 8.8 mg.; cephalin flocculation, 4 plus; thymol turbidity, 6.6 units and total protein, 5.8 with albumin, 2.6 and globulin, 3.2 gm. per cent. The electrophoretic pattern of gamma globulin accounted for 35 per cent of the serum protein. Because of the inadequate response to the

low salt diet and ammonium chloride, the latter was replaced by Diamox. On the 4th day of therapy he quietly went into coma. There appeared to be no premonitory symptoms.

In one patient paracentesis with the removal of 9.5 liters of fluid over a 6 hr. period was followed by coma. This 52-year old male was admitted with abdominal pain and ascites. Paracenteses had been performed elsewhere at least twice. At this time he presented with icterus, gynecomastia, palmar erythema and enormous abdominal distention. Hepatomegaly could not be definitely determined because of the ascites. Serum bilirubin was 5.8 mg.; total protein, 5.9 gm. per cent with 2.9 albumin and 3.0 globulin; alkaline phosphatase was 6.1 BU. Because of the huge collection of ascites, paracentesis was performed slowly. Nevertheless coma developed approximately 2 hrs. following the termination of the procedure preceded by mental disorientation and tremor.

I would like to add some comments on our studies of serum ammonium in patients with liver disease. [The recent observations that serum ammonium levels are elevated in hepatic coma has served as a vigorous stimulus to the study of the liver.] These studies have led to some conclusions but the picture is by no means clear cut. In the first place it is quite obvious that the disturbance in serum ammonium levels is only one of the many metabolic and electrolytic abnormalities that occur in this disease. It may be that some nitrogenous substance other than ammonia is the toxic material. There are many other factors to be considered which we hope to investigate later.

The biochemistry of serum ammonium and its relationship to hepatic coma goes back to the Krebs cycle. It has been postulated that ammonium combines with alphaketoglutaric acid and decreases the amount of this metabolite available for the Krebs cycle. The administration of glutamic acid by combining with ammonium produces glutamine and frees alphaketoglutaric acid for its normal metabolic role in the physiology of the brain cell[6,7]. An excess of ammonium in the brain depresses cerebral metabolism and is associated with mental confusion, disorientation, tremor and finally unconsciousness.

Serum ammonium in our laboratory has a normal range of 1-2.5 mcg.[8]. We employ the Conway microdiffusion technic as modified by Seligson. We are, however, unable to elaborate on the significance of elevations above 3 mcg. Other workers consider anything above 3 mcg. significant in so far as impending or actual coma is concerned and therapeutically significant also, in the sense that monosodium glutamate should be administered[1b,9]. We have found no such clinical correlation. Patients with severe liver disease, decompensated with ascites or jaundice, or compensated, were found to have serum ammonium levels up to 6 mcg. with no evidence of mental confusion or impending coma. Again, some patients following bleeding from esophagogastric varices with moderately large quantities of blood in their intestinal tract have yielded serum ammonium levels of 5 or 6 mcg. with no tremor or any evidence of coma.

Unfortunately the number of patients with coma in this series who have been studied, is not large. Yet, from the serum ammonium levels in 8 patients that varied from 5-12 mcg. we have been unable to establish any critical level of blood ammonium beyond which coma ensues. It may be that the peripheral venous blood levels fail to reflect a specific change in the ammonium metabolism of the brain cells. It may be as Bessman claims[7] that serum ammonium levels from arterial blood are more significant but most investigators are using venous blood determinations. In two patients in hepatic coma, the serum ammonium levels rose to 11 mcg. and 12 mcg. respectively and it may be that our estimate of normal values must be raised.

Although we have presented ammonium chloride as a primary or contributory factor in the development of coma, we attempted to induce hepatic coma in 3 patients with portal cirrhosis following the administration of 5 gm. of the salt t.i.d. for 3 days. No abnormal neurological manifestation was observed although serum ammonium levels reached 5 and 6 mcg. Obviously the mechanism that produces coma in some patients requires further study.

As far as treatment is concerned we employed the usual therapy of large doses of antibiotics, intravenous fluids when necessary, copious enemas and general supportive treatment. We have administered glutamic acid* to 3 cases with coma, two precipitated by hemorrhage and one by paraldehyde. There was no lightening of coma or any improvement whatsoever in these patients. One can argue obviously, that the presence of severe liver disease rendered the process irreversible, but, be that as it may, we effected no improvement; although in the case with paraldehyde we expected a good result. One must also note that the administration of 20 gm. of monosodium glutamate introduces approximately 150 mEq. of sodium into the electrolytic pool. The likelihood of producing respiratory alkalosis is not to be underestimated and careful observation of the patient during such administration is required. I must admit that while some investigators have had experiences similar to ours, others have reported remarkably good results in the previously uniformly fatal outcome of hepatic coma.

Since this paper was presented, we have been successful in one patient in coma, who received 60 gm. salt per day for 3 days. Arterial levels of serum ammonium were 4.5 mcg.

Summary:—The precipitating factors in the development of hepatic coma in 20 patients are reviewed. Hematemesis and infection remain the two most common causes. Ammonium chloride, narcotics and paracentesis are very occasionally responsible. Orally ingested protein, methionine, however, and intravenous Amigen appeared to be implicated in precipitating hepatic coma in patients with severe liver disease. The significance of serum ammonium elevations are briefly discussed.

*As monosodium glutamate generously supplied by the Abbott Laboratories 20 gm./dose.

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Discussion

Dr. Stanley H. Craig (New York, N. Y.):—First I should like to make mention that Dr. Friedman has really tackled a very difficult problem, and he has done a good job. We have all known for a long time that those patients who go into hepatic coma rarely, if ever, finally come out. They may come out and have remission, but rarely do we get a survival.

In studying some of the precipitating factors, Dr. Friedman has listed the hemorrhagic manifestations, hematemasis, melena, etc. His figures more or less are similar to those that are found in other hospitals, 5 out of 20, I believe, and some of them range up to 30 or 35 per cent. I would say that most investigators have found the same figures.

In the cases that Dr. Chaikin presented last year at the meeting, he also listed many cases of hemorrhage, and though he gave glutamic acid and had very fine results, they were only temporary. He noted that soon after the therapy, many of the cases developed hemorrhage, esophageal varices, and died.

The question that I bring up is that with the treatment by glutamic acid, with these spectacular results, we must realize they are only temporary and do not touch the liver disease. I believe that in these cases which go into coma, it is the severe liver disease, which is irreversible and that finally causes death. Even though this therapy may be on the right road, I do not believe it is the final conclusion that we are going to deal with, but we must find some type of therapy which will be permanent and not temporary. It is not life-saving.

In the case cited by Dr. Friedman, of the young man of 30 who survived the coma, I wonder whether he did not survive the coma for the simple reason

that his liver disease was not extensive but quite minor. With severe liver disease I doubt that that patient would have survived no matter what.

In the liver disease that we are dealing with for the most part, I believe Dr. Friedman will agree most of the cases are liver cirrhosis. In these cases of liver cirrhosis we have found about a third of them develop hemorrhage, and two-thirds develop a progressive failure of the liver. About a fourth to a third, by some investigators, have been found to develop concurrent infection which caused death. I think we have more or less come along with the figures of Dr. Friedman.

I was surprised that he had only one case of coma following paracentesis. At Metropolitan Hospital, here in New York, we have had a high percentage. Maybe it is because Dr. Friedman did not use paracentesis very frequently. I should like to know his opinion on that.

As to the narcotics being a precipitating factor, we know that morphine and other opiates should be avoided, because the liver is the normal site of detoxification. With severe liver disease these substances become toxic and coma might ensue. If a sedative should be given, might I suggest that the barbiturates be given, and stay away from morphine and its derivatives.

The only remaining question which I should like to discuss is the protein diets and the ammonia levels. We have found with protein diets the ammonia levels are elevated. If these elevations occur, I question the sagacity of giving the high protein diets in patients with liver disease, for I believe that will only send the patient into hepatic coma, and hasten the patient's death.

I again congratulate Dr. Friedman on his excellent presentation of this paper on a very difficult and interesting subject.

Dr. Max Caplan (Meriden, Conn.):—I should like to ask Dr. Friedman if he had any luck with the use of the steroids in hepatic coma. I mean any luck that was any better than the temporary luck some of us have had.

Dr. James T. Nix (New Orleans, La.):—Experimental evidence suggests that in dogs with hepatovenous congestion or cirrhosis, the ascitic fluid is extravasated hepatic lymph.

Dr. A. I. Friedman (Hackensack, N. J.):—I think it is important to distinguish between severe liver disease that goes into coma and severe liver disease that does not. I do not think it is just the severity of the liver disease. There are other factors involved here about which at the present time we do not know enough to put down any specific facts. We do know that given 2 patients, with apparently the same laboratory and clinical findings—one will have a hematemesis, a small hematemesis, his red blood count will drop a small amount, the hemoglobin perhaps 10 per cent, and he will go into coma. The other patient with the same manifestations will not go into coma. Why the difference between the two, I cannot at the present time tell you.

It may be that the chief factor is the presence of a shunt, and this has been shown to be true in the surgical shunts particularly. We had one patient who had had a successful portacaval shunt, and he was fed (purely for observation) a high protein diet. Within a period of two hours following the ingestion of the high protein, he developed mental disorientation. He didn't know where he was. He became confused and wandered around the ward and developed a tremor.

This has been observed quite frequently by others in the past two years. It is the old Eck fistula that we find in animals, and therefore we do know that the protein in these patients is toxic. Whether it is the ammonium ion or some other nitrogenous factor which is toxic, it is difficult to say at the moment because the investigation has not proceeded that far.

We have been looking for varices in these people to determine whether or not the indirect evidence of a collateral shunt was there. Unfortunately, our incidence of varices is not high, perhaps 20 or 30 per cent demonstrated varices in cirrhotics. Either we are not seeing the varices adequately or there are other factors involved.

We have attempted to discourage paracentesis, except in those patients who suffer severe respiratory embarrassment. Otherwise, we do not try to tap the ascitic. This procedure removes substances that the patient needs, especially albumin, from the homeostatic and electrolytic pool, and a lot of other elements, and you are actually decreasing the chances of the individual for a good therapeutic result. Hence, that is perhaps one of the reasons why we haven't seen as many incidents of hepatic coma following paracentesis.

If we have to do paracentesis, we do it very slowly, leaving the tube in and having it run for several hours.

We have no hesitancy in using chlorpromazine in patients with severe liver disease. I think the incidence of it causing jaundice is quite low, and if an occasional patient will get it, it certainly is a risk, but I think the risk is less than with barbiturates or with morphine, or any of the other sedatives. I think Demerol has been suggested. I feel, however, that with chlorpromazine we do get a much greater tranquilizing effect and we have not seen any jaundice in those cirrhotics who have received chlorpromazine.

We have not yet used any of the other tranquilizers like Miltown, etc. We are in the process of doing so now.

So far as the steroids are concerned, we have had the same experience as a lot of other people—no benefit, and in one case, where one of the interns got the dose somewhat confused—intravenous administration of a large dose over a period of approximately one hour, the infusion was really pumped into this patient—I think it was 100 units—there occurred a sudden massive hematemesis and exitus. Whether, however, that would have occurred spontaneously or not, I cannot tell you.

I want to thank the discussors for their kind and considerate comments and their contributions to this discussion.

STUDIES OF THE UNKNOWN FACTORS IN DUODENAL ULCER*

Hypoglycemia as a Possible Etiological Factor

MAXWELL BERRY, M.D., F.A.C.G.

Atlanta, Ga.

After reading Sippy's work published in 1915[1] and comparing his results in the treatment of uncomplicated duodenal ulcer with mine, I reached the very uncomfortable conclusion that Sippy was doing about as good a job 40 years ago as I was doing then. I, therefore, decided to review as much of the

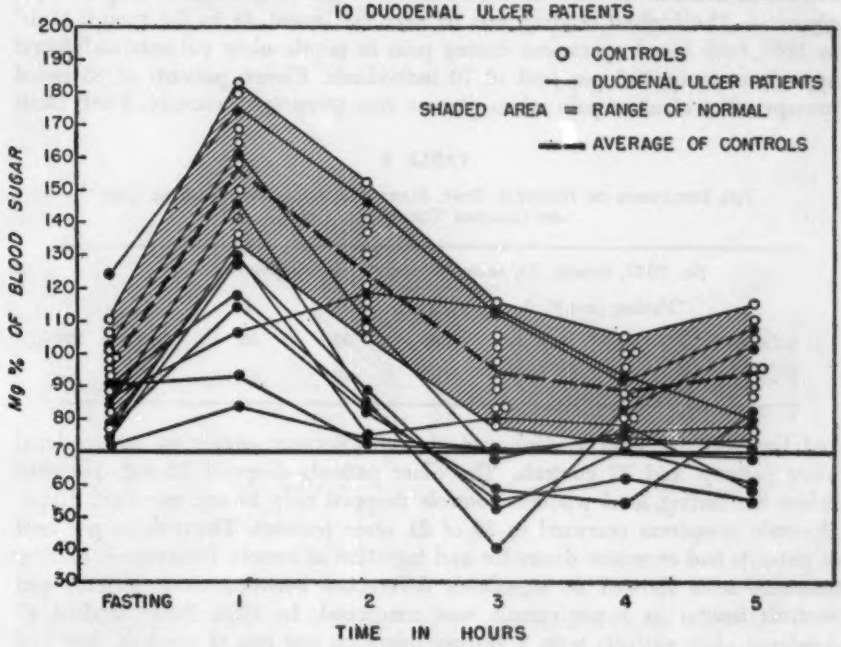

Fig. 1

literature since that time as possible and to attempt to keep my mind unprejudiced in a search for new etiological ideas or methods of treatment.

Running through the literature from 1920 on, there is a recurrent thread of suggestion that carbohydrate metabolism may be altered in peptic ulcer.

*Read before the Third Annual Convention of the American College of Gastroenterology, New York, N. Y., 15, 16, 17 October 1956.

Thus, Horgan[2] in 1920, found that 31 per cent of 71 patients with duodenal ulcer and 25 per cent of 71 with gastric ulcer showed hyperplasia of the Islets of Langerhans. This hyperplasia involved both the differentiated and undifferentiated cells. Straaton and Hunermann in 1936[3] and Christlieb in 1938[4] noted the frequent occurrence of hypoglycemia in peptic ulcer patients. In 1942, Evanson[5] ran three-hour glucose tolerance tests on 50 peptic ulcer patients and found that 16 per cent had hypoglycemia and that after gastric surgery, 27 of 70 patients with peptic ulcer had hypoglycemia. In 1945, Abrahamson[6] ran six-hour glucose tolerance tests on untreated active duodenal ulcer patients, and found that 12 patients with duodenal ulcer and 5 patients with gastric ulcer had hypoglycemia. Ten other duodenal ulcer patients in whom a single blood sugar was taken six hours after ingestion of 100 gm. of glucose developed hypoglycemia. The highest reading was 67 and the lowest 49 in the group. Muir[7] in 1949, took blood specimens during pain in peptic ulcer patients and found hypoglycemia in 28.3 per cent of 70 individuals. Eleven patients of 83 noted prompt relief of ulcer pain when glucose was given intravenously. Platt, Dotti

TABLE I

THE INFLUENCE OF HOSPITAL REST, SLEEP AND ADEQUATE GENERAL DIET ON GLUCOSE TOLERANCE TEST

No. 7847, female, 34, severe hypoglycemia symptoms 21 years						
	Fasting (hrs.)	1	2	3	4	5	6
8-29-56	88	53	46	62	46	31	62
9-13-56	94	157	117	112	81	96	–

and Beekman[8] in 1949 studied oral glucose tolerance curves on 30 duodenal ulcer patients and 32 controls. The ulcer patients dropped 31 mg. per cent below the fasting level whereas controls dropped only 19 mg. per cent. Hypoglycemic symptoms occurred in 20 of 21 ulcer patients. Thirty-three per cent of patients had excessive desire for and ingestion of sweets. Intravenous glucose tolerance tests showed no significant differences between ulcer patients and controls insofar as hypoglycemia was concerned. In 1954, Beck[9] studied 47 duodenal ulcer patients with a glucose tolerance test run at one-half, two and four hours after ingestion of 50 gm. of glucose. Fifty-one per cent of the patients showed hypoglycemia. Schlecter and Necheles[10], in a study of postprandial symptoms following subtotal gastrectomy for peptic ulcer, noted that while there were immediate symptoms, i.e. "dumping syndrome", another set of symptoms characteristic of hypoglycemia occurred one and one-half to three hours after eating. In 11 such patients studied, 10 showed hypoglycemia with blood sugars going to 50 or below after ingestion of glucose. The studies of Winklestein and Hess[11] and Muir[7] in 1949, showed that duodenal ulcer patients probably have an exaggerated sensitivity to insulin. Selye and his co-workers[12] in

1936 showed that insulin overdosage, like many procedures which produced hypoglycemia such as adrenalectomy, fasting, and partial hepatectomy, is particularly prone to cause severe gastric erosions in the rat. Selye and MacLean[13] found later that glucose administration by mouth or parenterally sufficient to keep the blood sugar normal or elevated, protects animals against stress ulcers produced by a host of different noxious agents. Poth and Fromm[14] in 1950 showed also that about 50 per cent of dogs sustained in hypoglycemia would develop peptic ulcers. A review of the incidence of peptic ulcer associated with diabetes shows that while one would expect an incidence of about 3.5 per cent[15],

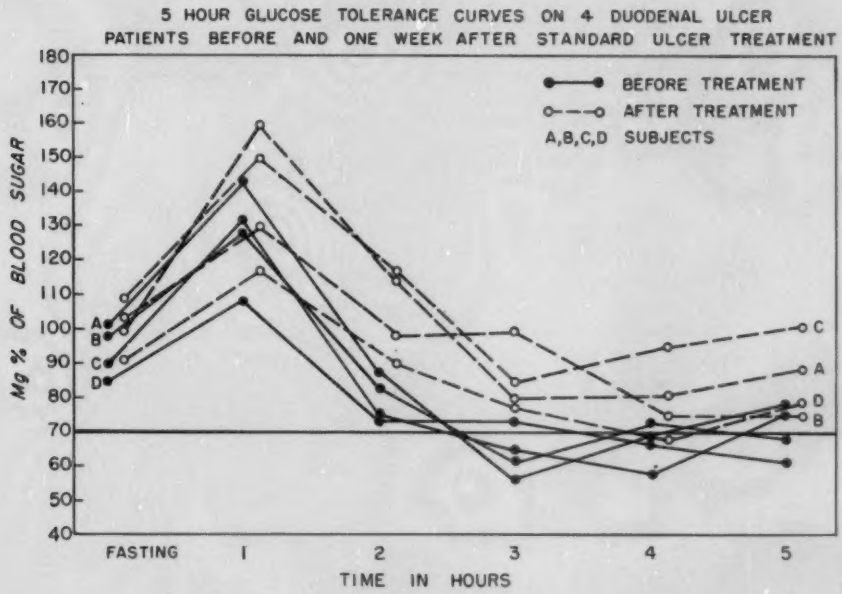

Fig. 2

it is actually much less i.e., 0.77 per cent[16-19]. No case of peptic ulcer was found in 4,103 diabetics before the use of insulin[17].

The physiological repercussions of hypoglycemia on the secretions of the stomach, the gastric tonus and peristalsis and by causing the release of epinephrine, probably on the gastric vasculature, should "set the stage" for peptic ulcer. Hypoglycemia by inducing gastric hypersecretion and hyperacidity[20], hypertonus and increased peristalsis[21,22], combine all those factors which are necessary to produce the "jet effect" found by Mann and Bollman[23] to be necessary in the experimental production of ulcer. Cannon[24] showed that when the blood sugar falls to between 80 and 70 in the animal, epinephrine is released.

Thus with blood sugars below 70, visceral vasospasm due to epinephrine might enhance the ulcerogenic effect of hypoglycemia.

It might be well to define what was meant by hypoglycemia in the above mentioned clinical studies. In all of them, 70 mg. per cent is taken as the lower limit of normal blood sugar. Figures less than this are assumed to be hypoglycemic. This is in accord with the findings of Joslin[16], Wilder[17], Cannon[19], Bulatao and Carlson[21], since the physiological repercussions of hypoglycemia start to occur at this level. I am well aware of the fact that since Seale Harris[25]

TABLE II

Author	Symptom	Duodenal ulcer patients	Controls
Joslin (16)	Sweating	3	0
	Nervousness	6	1
	Trembling	4	0
	Faintness	4	2
	Hunger	6	8
	Numb lips or tongue	1	0
	Tingling of lips or tongue	1	0
	Heart pounding	2	0
	Diplopia	0	0
	Dizziness	3	0
	Unconsciousness	0	0
	Convulsions	0	0
Poe (35)	Epigastric burning	4	2
	Epigastric gnawing	4	0
	Epigastric fullness	0	0
	Epigastric pain	3	0
	Flatulence	2	2
	Nausea	2	0
	Sour Stomach	1	1
	Nightmares	0	0
	Night sweats	0	0
	Headaches	5	2
Total		51	17

popularized spontaneous hypoglycemia, many excellent clinicians have had grave doubts as to whether any such entity really occurs. Thus, Alvarez[26] believes that low blood sugar in a tense, neurotic individual, like a low systolic blood pressure may not be the cause of the condition, but the result of it. I am heartily in accord with this concept, having rarely seen spontaneous hypoglycemia except in a person under stress or who is constitutionally inadequate. We must, however, remember that the physiological repercussions of hypoglycemia are harmful to ulcer and begin to occur when the blood sugar falls to a level

of 70. The effects on the stomach are just as bad whether the hypoglycemia is a cause or effect.

In my experience, there is a syndrome which is frequently found in clinical practice occurring primarily in tense, neurotic, or constitutionally inadequate people and those with peptic ulcer, wherein the fasting blood sugar is normal, but somewhere between the third and the fifth hour after ingestion of 100 gm. of glucose, the venous blood sugar falls to levels below 70. Coincident with this, the patient complains of weakness, trembling, headache, sweating, palpitation of the heart or blurred vision. Intravenous injection of sugar relieves the symptoms within 30 seconds and injection of 10 units of insulin intravenously when the patient is fasting and symptom-free, will induce the symptoms. A high carbohydrate diet, inadequate sleep, overuse of coffee, colas or tea and emotional stress will aggravate the condition while a high fat, high protein, low carbohydrate diet, mild sedation, anticholinergic drugs, mental tranquility and avoidance of cerebral stimulants, will improve it. Prolonged fasting causes

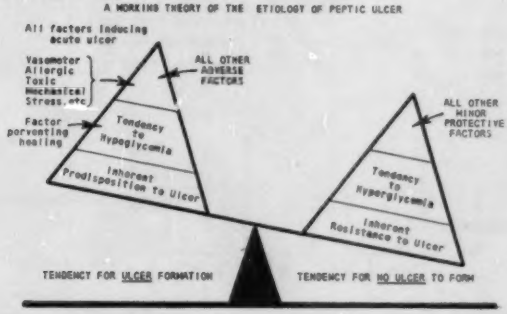

Fig. 3

neither hypoglycemic symptoms nor a drop in the blood sugar below 70. This syndrome is classically described as "functional hyperinsulinism" by Duncan[27] and Harris[25]. I am not concerned as to whether this syndrome is organic or functional, though I believe it to be the latter. I am concerned with the fact that when the blood sugar gets below 70, baneful physiological repercussions occur on the stomach.

A review of the first six clinical studies above showed that only Abrahamson[6] specifically stated that his peptic ulcer patients had been untreated at the time that six-hour glucose tolerance tests were run. The rapidity with which spontaneous hypoglycemia may be ameliorated by even bed rest, mild sedation[25], and a general hospital diet, (see Table I for a striking example of this) made it seem possible that the other studies were marred by failure to select completely untreated patients. In Figure 1 are summarized my findings in 10 untreated active symptomatic duodenal ulcers without complications and with a

crater or grossly deformed, sensitive duodenum by x-ray. The 10 controls were drawn from approximately the same age group and rigidly selected for absence of symptoms of hypoglycemia, no sign of significant organic disease from general examination and routine laboratory work, and with no familial history of peptic ulcer. As will be noted, 7 of the 10 duodenal ulcer patients showed definite hypoglycemia and another showed such an abnormally low, flat glucose tolerance curve that he probably should be included. Thus, in this small but rigidly selected group of duodenal ulcer patients, at least 70 per cent showed blood sugar evidence of hypoglycemia. In Table II are summarized the symptoms suggestive of hypoglycemia which occurred during the five-hour glucose tolerance test in the ulcer patients and in the controls. The controls had 17

TABLE III

Symptom	Before treatment	After treatment
Sweating	2	0
Nervousness	2	1
Trembling	2	0
Faintness	1	0
Hunger	3	3
Dizziness	1	0
Epigastric Discomfort	2	1
Nausea	1	0
Headache	3	1
Total	18	6

symptoms which might be related to hypoglycemia while the ulcer patients had 51 such symptoms.

In order to further test the hypothesis that the standard ulcer treatment might improve hypoglycemia, four patients with typical active duodenal ulcers and with a positive x-ray, who had hypoglycemia, were placed on a standard ulcer program consisting of either Pro-Banthine or Pathilon (anticholinergics) with phenobarbital before meals and at bedtime; Mucotin tablets (antacid), two every two hours when awake, an ambulatory ulcer diet with a half glass of milk and cream between meals and at bedtime and one Unicap a day. They were so treated for one week, then all medications were stopped for 36 hours before a second glucose tolerance test. The results are shown in Figure 2 and reveal that in every instance there was a shift upward toward normality in the glucose tolerance curve. Concomitantly, there was improvement in symptoms

suggesting hypoglycemia. The number of such symptoms decreased from 18 before treatment to 6 after treatment (Table III).

Early in the course of this investigation, after reading Abrahamson's paper[6] wherein he found that all of 27 patients with peptic ulcer had hypoglycemia, I began to wonder why peptic ulcer patients in the past had not given me a good history for hypoglycemia if it was present. Accordingly, in the next 41 intelligent patients with proved duodenal ulcer who came to me, I have taken first, a careful narrative history from the patient, and then specifically questioned him in regard to hypoglycemic symptoms. It was found that the symptoms of duodenal ulcer frequently mask those of hypoglycemia and only specific questioning will elicit the hypoglycemic symptoms. Of the patients so questioned, only five volunteered hypoglycemic symptoms, (other than those relating to epigastric discomfort) suggestive enough to make one think of hypoglycemia. Four patients noted headache relieved by food. Three noted "weak trembles". Four noted that nervousness was relieved by food, and one had night sweats. When specifi-

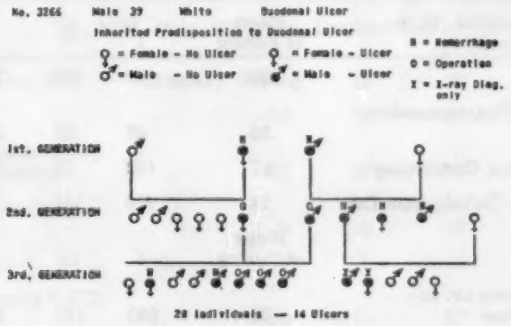

Fig. 4

cally questioned, however, 24 gave a good history for hypoglycemia, 6 gave a fair history and 5 gave a suggestive history. Six admitted to no symptoms other than abdominal pains. This is in accordance with findings of Evanson[5], Abrahamson[6], Muir[7], and Beck[9]. I fully realize the pitfalls in this type of interrogation and to the best of my ability avoided "putting words in the patient's mouth". Often even symptoms such as severe faintness, weakness, cold sweats, trembling or headache were not volunteered by the patient, but were readily elicited on specific questioning.

Eusterman[28] has postulated that three factors are necessary for the development of a chronic peptic ulcer. First, an acute ulcer or erosion; second, an inherent predisposition to chronic ulcer formation and, third, some factor which prevents the acute ulcer or erosion from healing. The wide variety of noxious agents and situations which can produce acute erosions or ulcers is well known and summarized by Mann[29] and by Selye[30]. It seems possible that hypoglycemia

may be a significant factor in preventing such acute erosions from healing, since all the physiological effects of hypoglycemia are such that they should be harmful to an ulcer, and since induced hypoglycemia in animals can produce not only acute ulcers, but if sustained, chronic duodenal ulcers indistinguishable from those in humans. Such a concept is illustrated in Figure 3.

The following case report of a 39-year old white office worker seems to exemplify all three factors. His chief complaint was abdominal pain, typical of peptic ulcer, located in the epigastrium radiating to the back and relieved especially by milk. He also stated that he developed attacks of the "weak trembles" with "cold sweats" and blurring of vision, usually preceding the ulcer pain, which were also relieved by milk.

TABLE IV

No. 3266, Male, 39, White, Duodenal Ulcer

Oral Glucose Tolerance Tests— 100 Grams Venous	Hours of Fasting	1	2	3	4	5
Initial Test	92	110	102	76	60	60
6 Mos. After Post. Gastroenterostomy and Vagotomy	86	97	53	33	73	83
1 Yr. After Subtotal Gastrectomy	97	130	53	76	90	90
1 Wk. After High Carbohydrate Diet	74	210	111	37	62	–
	Hours of Fasting	1	1½	2	2½	3
100 gm. CHO Given I.V. in 10% Sol. in 1 Hour	68	240	120	58	27	28
	Hours of Fasting	14	16	18	20	22
Blood Sugars Fasting		80	80	74	75	74.5

Of 28 known individuals in three generations of his family, 14 had ulcers as shown in Figure 4.

This unfortunate individual was married to a nagging, domineering, sexually frigid wife, who engendered enough resentment, anger and frustration in the patient, to produce acute erosions in anyone's stomach. After six months of intensive standard ulcer treatment without much improvement, a gastroenterostomy and vagectomy were done in 1949. He did not do well until 1951 when he found his marital situation intolerable and obtained a divorce. Following this, he seemed much better emotionally adjusted for several years. The symptoms of hypoglycemia continued, however, and ulcer symptoms recurred culminating in a severe hemorrhage. In 1954, he underwent a subtotal gastrectomy

with complete relief of ulcer symptoms, but marked exacerbation of hypoglycemic symptoms.

Glucose tolerance tests done over a period of years are shown in Table IV. The hypoglycemia seemed to be aggravated by posterior gastroenterostomy and eventual subtotal gastrectomy. One and a half hours after 100 gm. of carbohydrate intravenously, with a blood sugar of 27, he almost went into shock, became confused, disoriented, and dripped with sweat. Fasting blood sugars taken at two-hour intervals, however, 14 to 22 hours after fasting showed no level below 70 and no significant symptoms of hypoglycemia.

Table V shows gastric analyses done at varying times during his course and it is interesting that the initial tests showed a relative hypoacidity and that a gastric analysis during a glucose tolerance test following subtotal gastrectomy showed 20 degrees of hydrochloric acid an hour after the blood sugar had been recorded as 37 mg. per cent whereas histamine provoked a maximal free acid

TABLE V

No. 3266, Male, 39, White, Duodenal Ulcer

Gastric Analyses—Free HCl	(Minutes)	Fasting	15	30	45	60
Initial Test Meal		29	9	18	18	14
After Post. Gastroenterostomy and Vagotomy Histamine		25	32	55	55	68
After Subtotal Gastrectomy (75%) Histamine		0	0	2	4	4
	(Hours)	1	2	3	4	
Gastric Analysis During G.T.T. Blood Sugar		210	111	37	62	Mg. %
	Free HCl	0	0	4	20	Dgs.

of only 4 degrees. This would indicate that his spontaneous hypoglycemia was far more effective than histamine in causing the remnant of his stomach to secrete acid.

At present, he is on a high protein, high fat, extremely low carbohydrate diet, with milk and cream feedings twice between meals and at bedtime and on the anticholinergic drug, Pathilon, before meals and at bedtime. Symptomatically, he has shown a very marked improvement on this program. It has been my clinical impression that peptic ulcer patients do much better on a low carbohydrate, high protein, high fat diet, than when carbohydrates were not limited.

In summary then, the following conclusions seem justified:

1. Prior studies have shown that when the blood sugar falls below 70, physiological repercussions occur which should be harmful to peptic ulcer.

2. Hypoglycemia occurs frequently in peptic ulcer. Each of 9 prior clinical studies showed hypoglycemia (blood sugar 70 mg. per cent or below) to be present in a percentage of duodenal ulcer patients varying from 16 to 100, average 35. My study indicated a 70 per cent incidence.

3. Symptoms of hypoglycemia occur far more frequently in duodenal ulcer patients than in normal controls during a glucose tolerance test.

4. Previous animal experimentation has shown that hypoglycemia can produce peptic ulcers; and that it markedly sensitizes an animal to other ulcerogenic agents. Conversely, maintenance of a normal blood sugar markedly protects against experimental ulcers. In humans, diabetes exerts a protective influence on the development of peptic ulcer.

5. Therefore, spontaneous hypoglycemia may be one of the prime unknown factors in the etiology and recurrence of duodenal ulcer.

6. In future studies of carbohydrate metabolism in patients with peptic ulcer, patients should be untreated prior to study since treatment rapidly improves hypoglycemia, and controls should have no family history of ulcer or symptoms of hypoglycemia.

Summary

1. A review of pertinent literature is presented.

2. Significant hypoglycemia is defined.

3. Hypoglycemia was found in 7 of 10 duodenal ulcer patients and none in the controls.

4. Standard ulcer treatment tends to relieve hypoglycemia.

5. Ulcer symptoms seem to mask those of hypoglycemia.

6. A case report is presented showing a hereditary predisposition to ulcer, severe emotional stress as probable cause of acute erosions or ulcers and hypoglycemia as a possible factor in preventing the acute ulcer or erosions from healing.

7. Hypoglycemia may be one of the unknown factors which prevent acute ulcers or erosions from healing.

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Discussion

Dr. Max Caplan (Meriden, Conn.):—I want to thank Dr. Berry for allowing me to read this very interesting paper, and also for allowing me to hear his delivery and see these very interesting slides.

I have very little to say about this, since I have never made any special study similar to the one he made; however, there are a few points I should like to comment on. Perhaps the one which I should comment on most is the first statement in his really good paper, in which he said that after reading several reports by Sippy, 40 years ago, he found very little difference in his results in the treatment of peptic ulcer from those which Sippy obtained.

I think most of us will agree that the treatment of uncomplicated ulcer depends on long-established principles and not on some new wonder drug which has not yet been discovered and probably will not be discovered. I think those of us who feel that way are not too dissatisfied with the treatment of uncomplicated duodenal ulcer.

I firmly believe that only 10 to 15 per cent of patients with uncomplicated duodenal ulcer become complicated and that of those, only a very small percentage become, either after surgery or before surgery, ulcer cripples, so I think that our results with the treatment of duodenal ulcer are not too bad, and I think that we should not be ashamed of them.

I do feel, as Dr. Berry does, that there are some clinical factors which tend to prevent healing and perhaps to cause recurrence in a few of our patients, and that is why I think papers such as his are of very great importance. That is also why I think investigations along this line should be continued.

In looking up some of the literature on this, I was pleased to find out that one of the past secretaries of this organization, Dr. A. X. Rossien, had done some work along a similar vein and had proven that the instillation of glucose into the duodenum in uncomplicated ulcer patients prevented the increases in gastric acidity sometimes associated with recurrence. He did this when he was investigating enterogastrone and it was just mentioned in an aside.

Also it should be remembered that some of the newer anticholinergic drugs which we have a tendency to lean on, do not prevent the production of acid when insulin is used to produce hypoglycemia. In a recent article by Kasich, on the use of Tricyclamol, he specifically mentioned that this drug did not prevent insulin hypoglycemia from producing increased acidity. Furthermore, it should also be remembered that some of these newer drugs which have now been placed on the market which are being used as adjuncts or substitutes for insulin, have different mechanisms of action, and sometimes do not prevent the production of insulin-produced hypoglycemia and subsequently increased acidity.

After listening to this paper, I myself am going to pay a great deal more attention to some of these precipitants of hypoglycemia present in ulcer patients, so well shown by Dr. Berry, and I am more impressed with some of the principles laid down in the treatment of duodenal ulcer in which there was a high protein, low carbohydrate diet with anticholinergic drugs.

Dr. C. Wilmer Wirts (Philadelphia, Pa.):—I am pleased to be able to discuss this paper because I think it is wise to review periodically our concept of the etiology of ulcer. It is important to bear in mind that all treatment today, whether it be medical or surgical, is based upon a theoretical concept of the etiology of ulcer. That perhaps in itself would justify Dr. Berry's adding another facet to our thinking about a disease where we are still seeking the cause.

As he pointed out, it has been demonstrated, both experimentally and clinically, that there appears to be some relationship between the ulcerogenic mechanism and the metabolism of sugar. Whether this is due to hyperinsulinism as a result of increased pancreatic function, or other cause is still, I think, an open question.

It is agreed, I believe, among most investigators that severe changes in gastric or gastroduodenal physiology, will result from the inducement of hypoglycemia as a result of insulin administration.

Our own interest has been attracted to this during the past two years while investigating the mechanism of gastrointestinal bleeding. Following the administration of histamine and insulin, according to the method suggested by Jerzy Glass, we noted among other things, in the patient with an active or quiescent ulcer, that there is accumulation of gross blood in the stomach, in contradistinction to the nonulcer subject. It is of interest that the most pronounced effect occurs with the maximum hypoglycemia. At the moment one can only speculate about the significance of this observation, but the capillary permeability of the ulcer patient appears to be increased and there appears to be some relationship to hypoglycemia.

Whether we should interpret the observations of Dr. Berry at the moment, from the standpoint of clinical application, may represent another question. I remember very well an interesting panel at the American College of Physicians, in Boston, when Dr. Ingelfinger was asked about the effectiveness of a given therapeutic measure for ulcer. He replied that ulcer is one of the 70 per cent diseases, and probably 70 per cent of patients will respond to anything we give them. Therefore I think it is important that we do not go beyond the fact that this is an observation which deserves more attention. It should stimulate us to look for these factors in our own patients, and to be guided accordingly. To use this data as a basis for specific therapy, may be putting the cart before the horse.

In conclusion, I want to ask Dr. Berry two questions—perhaps three. He has pointed out that hypoglycemia may have something to do with the development of ulcer, therefore, why do we not find a high incidence of ulcer in cases of hyperinsulinism, due to island cell adenoma? Furthermore, if there is some relationship of hypoglycemia to ulcer, can it be demonstrated by histologic study of the pancreas, or is it a manifestation of hypoglycemia developed in some other system or organ, the liver perhaps?

Finally, if hypoglycemia is essential to ulcer formation what is the relationship of the non-beta cell adenoma of the pancreas described by Zollinger, et al. These cases had, as you know, severe ulceration but to my knowledge did not have hypoglycemia.

Dr. Maxwell Berry (Atlanta, Ga.):—The first question is "Why is the incidence of duodenal ulcer low in hyperfunctioning islet cell adenomas if spontaneous hypoglycemia tends to produce duodenal ulcers?" I don't know the answer, but perhaps, as Eusterman postulated, an inherent predisposition to chronic ulcer formation is required in the individual before he can develop chronic duodenal ulcer. This predisposition seems to occur in about ten per cent of the population. One would, therefore, expect the maximal incidence of ulcer due to hypoglycemia to be about ten per cent. Actually, we now have about 35 cases of peptic ulcer in about 450 cases of islet cell adenoma—an incidence of about seven to eight per cent. This is about double the expected incidence of ulcer in the general population, i.e., 35 per cent. Also, there may be a fundamental difference in the response of the body to hypoglycemia induced by an insulinoma and that induced by spontaneous hypoglycemia. In the insulinoma, overproduction of insulin starts gradually and steadily increases, thus, allowing the full development of homeostatic mechanisms. On the other hand, the intermittent and transient nature of spontaneous hypoglycemia may not produce such homeostasis.

I do not know the answer to the second question.

The third question is, "Why do some of the worst peptic ulcers occur in nonfunctioning islet cell adenomas?" Again, I do not know the answer, but might guess that most of the so-called "nonfunctioning" adenomas started out as insulinomas, and later became carcinomas. Thus, in the 29 cases collected by Ellison, there were six definite cases with hyperinsulinism, 17 were not studied for hyperinsulinism and may or may not have had it and 20 cases had islet cell carcinomas. The latter group may have started as insulinomas and lost their insulinogenic function in undergoing malignancy or again, the homeostatic mechanisms may have overcome hypoglycemia. The occurrence of seven cases with adrenal cortical or medullary or anterior pituitary adenomas or hyperplasia lends some weight to the latter speculation.

COMPLETE NUTRIMENT FOR THE THERAPY OF PEPTIC ULCER—FURTHER STUDIES

Sustagen Therapy of Peptic Ulcer

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Whatever the underlying cause or causes of peptic ulcer, it is generally agreed that the immediate precipitating factor is physicochemical action, i.e., the effect of free hydrochloric acid and pepsin on a susceptible mucosa. As a result of this concept, most ulcer regimens attack the "acid" or "peptic" factor. For this purpose, a therapy that provides a bland, high-caloric and high-protein fluid, with neutralizing properties superior to milk, would seem to possess the elements of an ideal ulcer therapy.

Recently, a high-caloric, high-protein nutrient powder* was introduced which has proved eminently satisfactory for that purpose. This complete nutriment is available in powder form and is easily miscible with water to form a liquid emulsion. One hundred grams of the powder supply 390 calories, 24 per cent of which are from protein, 8 per cent from fat, and 68 per cent from carbohydrate. In addition, it contains the known essential vitamins and minerals in generous amounts. An analysis of the properties of this preparation suggested that it might prove of considerable value in the care and dietary treatment of patients with peptic ulcer.

Among the characteristics of the complete nutriment that suggest its usefulness in ulcer therapy are: 1. neutralizing ability, 2. high-caloric, high-protein value, 3. generous mineral and vitamin content, 4. fluid nature, and 5. satisfactory palatability.

In a preliminary study[8], the acid-neutralizing property of the complete nutriment was compared with whole milk in a group of 30 patients with gastric hyperacidity. It was found that whole milk administered orally to these patients failed to control the gastric acidity to a clinically satisfactory degree. The oral administration of 8 oz. of the complete nutriment mixture, on the other hand, was followed by achlorhydria for one to two hours (usually one and one-half hours). It was also found that intragastric night drip of the complete nutriment produced a continuous absence of free hydrochloric acid. As a result of these studies, a clinical trial of the complete nutriment in the treatment of uncomplicated duodenal and gastric ulcers here reported was instituted.

*Sustagen supplied by Mead Johnson & Company, Evansville, Ind.

Clinical Material

The patients were from the private practice of the author and included 33 with duodenal ulcers, 4 with gastric ulcers, 2 with combined duodenal and gastric ulcer, 2 with jejunal ulcer (1 after gastroenterostomy and 1 after subtotal gastrectomy), 1 with peptic esophagitis (with a hiatus hernia), and 1 esophageal ulcer (with a hiatus hernia), in a total of 40 patients. In order to give our therapeutic program a drastic test, patients whose ulcers had proved refractory to conventional measures including anticholinergic drugs, liberal ulcer diet, and nonabsorbable alkalis were chosen for therapy. The average duration of symptoms in the group studied was 6.8 years.

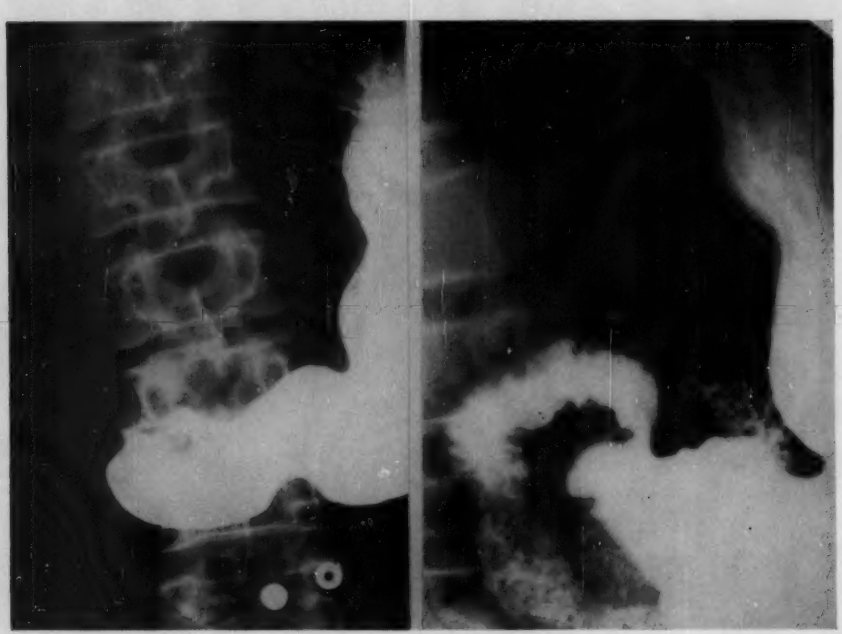

Fig. 1—(Case 1) Large prepyloric ulcer crater (left) almost completely healed (right) in eight days.

Method of Therapy

Thirty-six patients were treated with oral therapy as described below. In 2 of these, the intragastric drip was also employed. The remaining 4 received continuous intragastric drip alone.

The mixture for oral therapy was prepared by placing 3 cups of the complete nutriment in 1 quart of water. Every two hours during the day for the first five days, 180 c.c. of this mixture was given. During the second 5-day period,

cooked cereal, eggs, and soft white bread and butter were added. After that, a liberal ulcer diet was allowed with the complete nutriment between the meals and before retiring. Patients who were awakened by night pain were advised to drink a glass of the complete nutriment in the aforesaid dilution. A small number of patients disliked the sweetness of the preparation. In such instances, flavoring with vanilla or bitter (or sweet) chocolate was permitted.

For patients who were given nocturnal drip therapy, the mixture was dripped into the stomach at 20 to 30 drops per minute, either through a 14

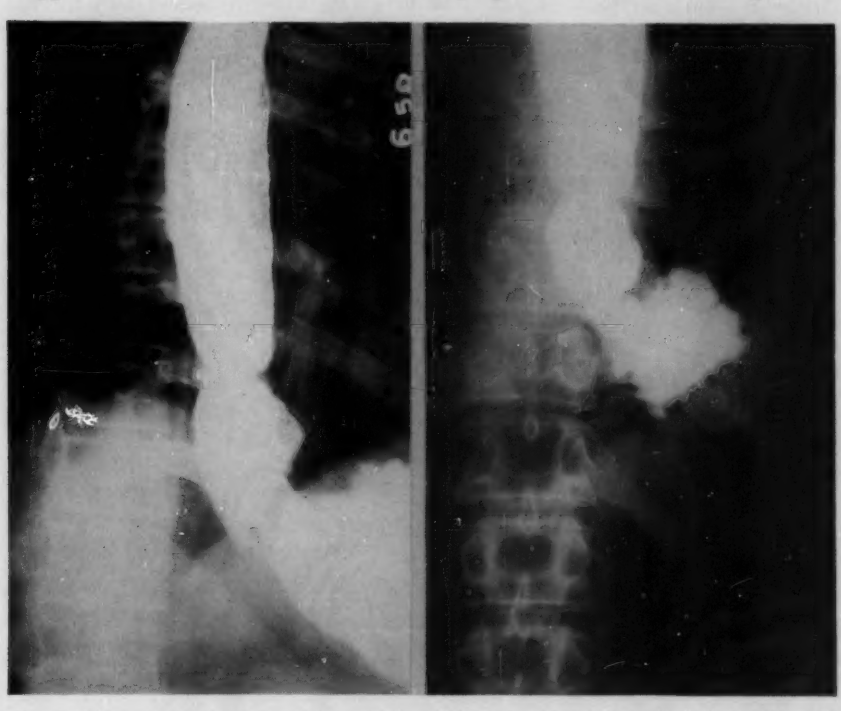

Fig. 2—(Case 2) Penetrating esophageal ulcer (left). Completely healed (right) with eight days of Sustagen oral and drip therapy.

French Levin tube or a thin polyvinyl tube* (nasally or through the mouth) for 8 to 10 days. These patients received the mixture used for oral therapy during the day.

Anticholinergic drugs and alkalis were not employed during the therapeutic program reported in this paper.

*Tube Feeding Sets (Mead Johnson & Company) were used.

Results

Good results were obtained in 35 of 40 patients, a favorable response rate of 87 per cent. Criteria of successful response included symptomatic relief of epigastric pain and discomfort, maintenance of weight or weight gain, and roentgenologic evidence of healing. In 2 patients, duodenal ulcers recurred in four months. A third case of duodenal ulcer was unrelieved by three weeks of the therapy and required a subtotal gastrectomy. A patient with combined duodenal and gastric ulcer developed pyloric obstruction after one month of freedom from symptoms. A patient with gastric ulcer remained well for two

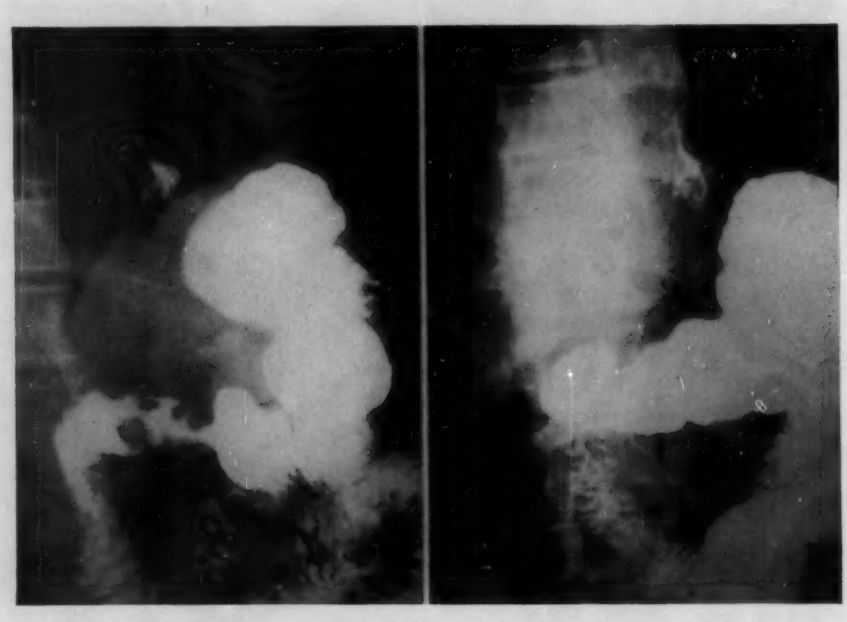

Fig. 3—(Case 5) Prepyloric gastric ulcer and duodenal ulcer (left). Both completely healed (right) with Sustagen therapy.

months and then experienced a massive hemorrhage. A subtotal gastrectomy was performed.

Miscellaneous Observations

In 18 of the patients with duodenal ulcers, radiographic examinations were carried out before therapy and at the end of one month of treatment. In 12 of these, the duodenal niche disappeared. In the other 6, the crater was not visible but the bulb remained deformed. The craters in 3 patients with gastric ulcer disappeared and diminished greatly in size in the fourth patient. The penetrat-

ing esophageal ulcer healed completely in eight days (with oral plus drip therapy).

Case Reports

Case 1:—C. K., male, age 61. The patient had experienced severe ulcer symptoms for eight months. X-rays revealed a large irregular crater in the antrum. In spite of gastric acidity pH of 1.5, a malignancy was strongly suspected. After eight days of the oral complete nutriment plus nocturnal intra-

Fig. 4—Duodenal ulcer (left) which healed completely (right) with three weeks of Sustagen therapy.

gastric drip, radiographs revealed complete healing of the ulcer crater (Fig. 1). The patient has remained entirely well for one year.

Case 2:—H. M., male, age 50. Severe substernal pain and dysphagia were present for four months. X-rays and esophagoscopy revealed a penetrating circular ulcer in the lower esophagus associated with a sliding hiatus hernia. X-rays after eight days of therapy (oral and drip) revealed a disappearance of the niche (Fig. 2). Esophagoscopy at that time demonstrated a linear scar. The patient has remained well for one year.

Case 3:—E. H., female, age 34. After two years of peptic esophagitis, an esophagogastrectomy was performed. Following this, severe symptoms of heart-

burn and dysphagia were present for one year. X-rays revealed irregular narrowing of the lower esophagus. The patient was maintained on oral therapy with the complete nutriment for one month with complete absence of symptoms. X-rays at the end of that period revealed a normal esophageal configuration. She has remained well for six months.

Case 4:—R. S., male, age 56. Severe ulcer symptoms had continued for six years. X-rays revealed ulcer crater in duodenal bulb and a gastric ulcer high

TABLE I

ACIDITY STUDIES

	Before Therapy pH	After 1 Month of Therapy pH
S.G.	1.5	3.0
E.L.	1.5	3.0
J.M.	1.0	2.0
M.P.	1.0	2.50
O.S.	1.0	1.5
O.F.	1.0	1.0
R.S.	1.0	2.5
S.S.	1.0	1.5
E.W.	1.5	1.5
M.A.	1.0	2.5
A.C.	1.5	1.5
L.G.	1.0	1.5
G.J.	1.5	1.5
B.K.	1.5	1.5

In 8 of the 14 patients in Table I, the pH was higher after one month of therapy with the complete nutriment.

on the lesser curvature. Both lesions healed completely after one month of complete nutriment therapy.

Case 5:—M. R., male, age 67. The patient had a history of a duodenal ulcer of three years' duration, now healed. Recently he developed a prepyloric ulcer which had caused severe discomfort for two months. On the basis of x-ray examination, a malignancy was suspected. After one month of therapy, the ulcer disappeared completely (Fig. 3); patient has remained symptom-free for three months.

Acidity Studies

In 14 cases of duodenal ulcer, the pH of the gastric contents was determined just prior to and one month following institution of the therapy with the complete nutriment. The determinations were made 45 minutes after a standard breakfast of tea and toast (Table I).

Follow-Up Studies

Thirty-nine patients were followed for one month to two years; 20 were observed from six months to two years.

Comment

The program of therapy presented here, while proving eminently satisfactory in the control of gastric acidity and in providing nutritional support for the patient, is not intended to exclude other measures of established value such as anticholinergic drugs, nonabsorbable alkalis, psychosomatic therapy, and indicated surgical measures.

In addition to affording local protection to the ulcerated gastric or duodenal mucosa, the complete nutriment systematically enhances healing of the ulcer and restoration of the patient to a state of optimal nutrition. The dynamic theory of metabolism informs us that there exists a large, labile pool of metabolic fragments stemming from the protein, fat, carbohydrate, vitamins and minerals of the diet. Also channeled into this pool are all of the materials derived from the degradation of body tissues. Physiologic repair is dependent upon a ready and constant supply of materials from this labile pool. The complete nutriment acts to replenish this pool and hence to indirectly protect against excessive tissue degradation by providing direct and cogent support to the physiologic processes of repair.

Conclusions

1. The immediate cause of peptic ulceration is action of acid plus pepsin on a susceptible mucosa.

2. Neutralization of free acid plus provision of good nutrition are basic in ulcer therapy.

3. The powdered complete nutriment accomplishes both of these basic objectives and is therefore a valuable therapeutic agent in peptic ulcer.

4. Thirty-five (87 per cent) of 40 patients who were refractory to conventional ulcer therapy including anticholinergic drugs, liberal ulcer diet, and alkalis responded favorably to this form of therapy, as shown by clinical, x-ray and laboratory evidence.

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PATHOGENESIS OF ALCOHOLIC HEPATITIS*

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Introduction

Cirrhosis is seen in multiple histologic forms. Characteristically, several of these processes are seen together. Usually associated are small areas of necrosis, cicatricial sclerosis and other areas of fibrosis, and irregular nodules of cellular hyperplasia. The abbreviated term "alcoholic cirrhosis" should be reserved for patients with the cirrhotic process who have had alcoholic hepatitis.

There is evidence that the precirrhotic process can be identified. With R. Dupuy, J. Herman and M. Corteville[7-11] we investigated cirrhosis particularly of hepatitic origin, by functional tests and repeated needle biopsies in order to study its pathogenesis.

Our anatomical and biological data includes 35 patients. Eleven of these have been previously reported[7,8]. Several modes in the pathogenesis of alcoholic hepatitis to cirrhosis were observed. It is now possible to describe a new histo-biological state in the pathogenesis of cirrhosis. This we call "subacute cytolytic or steatosic hepatitis".

Technic

Anatomical specimens were procured by needle biopsy and at laparotomy. Tissues were fixed in aqueous Bouin solution, in alcoholic Bouin solution, in Carnoy's fluid and in Regaud's fluid. Tissues were studied with five stains: Masson blue (hematoxylin, fuchsin-ponceau, and aniline blue) for the structure, Best's carmine for glycogen, Pappenheim-Unna (methyl green, pyronine) for ribonucleins, Regaud's hematoxylin with iron for chondrioma, and Folgen's stain for thymonucleins.

To evaluate liver function, multiple tests were done in accordance with the concept that "momentary hepatic status" (Noel Fiessinger and H. Walter) is of greatest value. Chemical studies were of three groups: 1. hepatic filtration (passage tests) 2. flocculation and 3. serum proteins and other tests.

*Revised by Julian A. Sterling, M.D., F.A.C.G., Philadelphia, Pa.

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Tests to determine filtration capacities ("passage tests")[3] included galactose tolerance, hippuric acid conjugation, and hepatic water flow rate.

Flocculation tests included thymol turbidity, zinc sulfate (Kunkel's) precipitation, Gros' reaction, Hanger's flocculation, and the red colloidal reaction. Serum proteins were determined chemically and by electrophoresis[30a]. Additional studies in individual patients included determination of bromsulfalein excretion, prothrombin time, serum cholesterol, phosphatase, lipase and bilirubin.

Normally, galactose excretion is complete within four hours unless there are defects in the absorption mechanism.

In the hippuric acid conjugation, Quick's classification is used. Normally more than 3 gm. of hippuric acid is eliminated in four hours.

Urine specimens were obtained at 2, 4, 10 and 24 hours for study of water passage simultaneously with the galactose tolerance test[24].

Various flocculation tests have been used in conjunction. Maclagan's thymol test was read from a Bonet-Mauri photoelectric meter with an attachment for reading opacity in red light (screen no. 15). The reading is expressed as Bonet-Mauri degrees which are approximately double the Vernes' degrees and eight times Maclagan's units. The normal figures are lower than 20°. The reagent was prepared in accordance with Huerga and Popper's modification[28a].

Kunkel's reaction to zinc sulfate was read from the photoelectric meter and expressed in Bonet-Mauri degrees. Normal level is less than 50°[29a].

Gros' reaction is normal when greater than 1.9 c.c.[26a].

Ducci's red colloidal reaction[6] is reported as a negative reaction when 1 or 2; doubtful reaction when 3; positive reaction when 4 or 5; The Sudan IV or scarlet red used was "cerol red" (R.A.L.) whose formula had recently been specially observed to give strongly positive reactions in patients having hepatic cirrhosis with mesenchymatous changes.

Histobiological Syndromes of Alcoholic Hepatitis

Three main forms of alcoholic hepatitis may be distinguished.

1. *Subacute noncirrhogenous alcoholic hepatitis:*—The hepatic parenchyma is preserved and the lobular structure is intact.

2. *Chronic cirrhogenous hepatitis:*—Initial anatomical stigmata of cirrhosis are present together with early disruption in lobular structure.

3. *Incipient cirrhosis:*—This is recognized histologically as an annular cirrhosis. Clinically, it is latent: there is no icterus, nor ascites, nor is there obvious portal hypertension. This state, however, is usually biologically decom-

pensated, since manometric and portographic signs of portal hypertension are present. It may be biologically compensated without any functional changes in the liver. This latter form constitutes the rare form of *residual cirrhosis.*

Each of these phases may be accompanied by superfluous fat, as a *steatosic* type, or superfluous fat may be absent as in the *cytolytic* type.

Each anatomical group above has individual functional capacity. Each of these will be described separately. We will also discuss the pathogenesis of cirrhosis through these phases to the decompensated form.

Subacute Alcoholic Hepatitis

Clinical examination in subacute alcoholic hepatitis usually discloses an isolated hepatomegaly without splenomegaly, or increase in collateral circulation. Even in the absence of hepatomegaly, there may be an abnormal weight loss or some, slight dyspepsia. Very often, this disorder is functionally latent.

More rarely, serious disorders including disorientation and tremors of neurologic origin, together with severe digestive symptoms, are present.

Subacute forms of hepatitis represent the early phases of the "alcoholic liver". This is true for subacute forms of both subacute cytolytic hepatitis (10 cases) and subacute steatosic hepatitis (12 cases). In these 22 cases, very clearly defined disorders in the hepatic filtration mechanism were observed. By contrast, flocculation reactions were normal, and chemical and electrophoretic patterns for serum proteins were subnormal. There are some slight differences between the cytolytic and steatosic varieties.

Subacute steatosic hepatitis:–Observations of hepatic filtration include opsiuria (less than 200 c.c. of urine in the first two hours) with oliguria seen in 7 of 12 patients. Galactosuria (more than 1 gm. galactose in the first two hours) was increased in every patient. Induced hippuricuria was abnormal in 5 of the 12.

Flocculation reactions on the other hand, were normal in almost every patient. Gros' reaction, was seen at the lower limit of normal. Maclagan's reaction was only slightly disturbed in three patients. The Kunkel and red colloidal tests were normal in all 12.

Serum protein levels were slightly decreased in six patients. Electrophoresis was abnormal in four patients: albumin was decreased to 45 per cent while beta and gamma globulins were increased to 20 or 25 per cent. In two patients the electrophoretic patterns were normal.

Subacute cytolytic hepatitis:–Alterations in hepatic filtration were present. Abnormal passage of water was seen in seven of the ten. Proiuria (more than 300 c.c. of urine in the first two hours when the patient has only taken 200 c.c.

of water) was as frequent as opsiuria. Galactosuria was, as in the previous type, disturbed in all patients. Induced hippuricuria was abnormal in five of the ten.

The flocculation reactions generally were normal. In one patient Maclagan's reaction was at the upper limit of normal. In another patient unexplained disturbances in Maclagan's, Gros' and red colloidal tests were present.

Serum proteins were decreased in six patients; serum albumin was decreased and the A/G ratio was correspondingly changed. Electrophoresis was abnormal in six of the ten patients. The albumin was lower while the beta and gamma globulins were higher. This was seen to be as in the steatosic variety. A rise, however, in alpha-2-globulins was frequently seen.

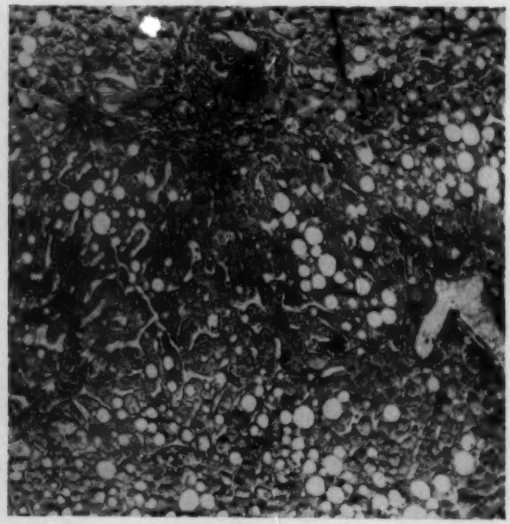

Fig. 1—(Case 13, Mr. C.) The histobiological syndrome of steatosic subacute hepatitis (Masson blue). Steatosis and "clear" cells plus neoform dark cells are seen histologically. Physiologically, this type reveals disturbances in hepatic filtration together with normal flocculation tests.

We have observed, then, that patients with subacute hepatitis (either cytolytic or steatosic) usually have a negative red colloidal reaction. This is a practical way to identify cirrhogenous hepatitis and incipient cirrhoses.

Although the laboratory tests are similar in the cytolytic and steatosic varieties there are histologic differences which may be observed.

Histology of subacute steatosic alcoholic hepatitis:—Generalized or patchy fat is present in the hepatic cells. In mild cases other changes may be seen adjacent to the fatty cells. These include: occasional "dark cells" which have a

normal nucleus and the "clear cells" which more often appear in the cytolytic form. This observation indicates the diffuse nature of the parenchymatous changes in the liver. Certain negative observations are important: there is no histologic sclerosis, nor is there an inflammatory cell reaction, nor can an alteration in the lobular structure be found (Figs. 1 and 2).

Case 13:–Mr. C. The laboratory findings in the case shown in Figure 1 were as follows: Total protein, gm./100–8.2; albumin–4.6; globulin–3.6; A/G ratio–1.27.

Electrophoresis:–Albumin–38 per cent; globulin $\alpha 1$–1.4 per cent; globulin $\alpha 2$–6.7 per cent; globulin β–23.8 per cent and globulin γ–30.1 per cent.

Flocculation tests:–Maclagan (°BM)–32; Gros (c.c.)–1.4; Hanger–+; Kunkel (°BM)–57; red colloidal–1.

	Ur	Gal	H.A.
2 hr.	145	2.07	2.57
4 hr.	175	0.99	
10 hr.	190	1.34	
24 hr.	800		
Total	1310	4.40	

The "clear cells" are deficient in mitochondrial elements and in ribonuclein granulations. The little "dark cells" show an abundant and dense chondrioma, abundant ribonuclein granulations and brightly colored large (red) nuclei which, are seen in early cell regeneration. The fatty cells, show, in the little residual crescent of protoplasm, mitochondrial elements and ribonuclein granulations held within the lipid vesicle. This indicates the superfluity of fat within the cell, rather than its degeneration.

In one patient under observation, the use of lipotropic substances (choline, methionine, and others) produced incipient cirrhosis[7]. In two patients the disappearance of the steatosis did not coincide with biological improvement. In these patients, a needle biopsy, later in the course of treatment revealed persistent nonsteatosic cytolytic hepatitis and "clear cell" infiltration. From these facts we observe that subacute steatosic hepatitis is a diffuse cytolytic parenchymatous hepatitis complicated by the temporary appearance of superfluous fat which may mask cellular changes.

Histology of subacute cytolytic hepatitis:–This is the purest type we know of diffuse parenchymatous hepatitis (Fig. 2).

The fundamental histologic anomaly is the presence of large number of "clear cells". These are large, and polyhedral. They compress the sinusoids so that the aperture is obliterated (Fig. 3). Cellular chondriome is rarefied and marginated around the nucleus. The cellular membrane is edematous. The protoplasm is deficient in ribonucleins (Fig. 4). Since, some cellular elements are paler than others a "ballooning" phenomenon is produced.

Bordering on the portal spaces, a few sparse neoform cells which are small and dark with a large nucleus, dense chondriome and abundant ribonucleins, bear witness to regenerative reaction. Here again there is no sclerosis, nor mononuclear inflammatory reaction, nor any modification in the structure of the lobule. Of course, steatosis is absent (Figs. 3 and 4).

Case 31:—Mr. L. In the case illustrated in Figure 3, the findings were: Total protein, gm./100—9.1; albumin—5.9; globulin—4.2; A/G ratio—1.4.

Electrophoresis:—Albumin—42.6 per cent; globulin $\alpha 1$—2.8 per cent; globulin $\alpha 2$—9.5 per cent; globulin β—20.2 per cent and globulin γ—24.7 per cent.

Flocculation tests:—Maclagan (°BM)—14; Gros (c.c.)—1.7; Hanger—0; Kunkel (°BM)—29; red colloidal—0.

	Ur	Gal	H.A.
2 hr.	75	1.14	1.42
4 hr.	200	1.42	
10 hr.	175		
24 hr.	320		
Total	770	2.56	

The term *cytolytic* was chosen to mark the fact that cellular changes in this lesion are not accompanied by either necrobiotic phenomena or by superfluous fat.

It is interesting to note that in these patients with purely cellular lesions without inflammatory reaction, the liver filtration tests alone are abnormal. The flocculation tests are normal.

The "clear cells" are also seen in viral hepatitis together with abnormal flocculations, reactions and changes in the electrophoretic protein pattern. This parallel observation leads us to the conclusion that it is the generalized cellular clarification which causes disorders in the hepatic filtration tests (water, galactose and hippuric acid).

This form of hepatitis may regress when the toxic element is eliminated and when certain drugs are used to protect the liver. Due to an insufficient

follow-up (ten months) we have been unable to prove this conclusively. It is possible that repeated damage causes cytolytic cirrhogenous hepatitis and cirrhosis; we have not so far had the opportunity of observing this transition positively.

Chronic Cirrhogenous Hepatitis

Clinically, these patients differ from those with subacute alcoholic hepatitis in several ways. First, in chronic cirrhogenous hepatitis, hepatomegaly is usually present and is accompanied by splenomegaly. In addition, there are more gastrointestinal symptoms. The diagnosis, however, may be differentiated

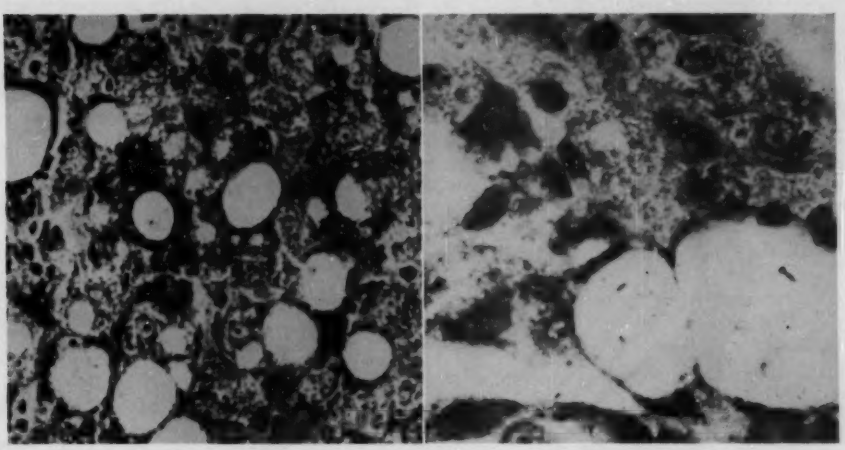

Fig. 2—(Case 13, Mr. C.) Cytological details of subacute steatosic hepatitis. *Right*, study of the mitochondria (Regaud stain) showing a. cells with excess lipids whose chondriome is driven back to the periphery, b. small, dark regeneration cells with dense compressed chondriome and c. light "clear" cells with rarefied chondriome.
Left, study of ribonucleins (Pappenheim-Unna stain) showing ribonucleins in the little, dark regeneration cells. Ribonucleins are present in decreased concentration in the clarified cells.

through laboratory tests and microscopy. Among the laboratory studies, the red colloidal reaction is always strongly positive (4 or 5).

Histologic changes are extensive and result in disturbance of the lobular structure. It is at this stage that the cirrhogenous process is evident.

In addition to these general findings, certain biological signs have enabled us[8] to distinguish two histologic forms of cirrhogenous hepatitis. These are the "steatosic" and "cytolytic" forms of cirrhogenous hepatitis.

Steatosic cirrhogenous hepatitis:—The steatosic form has a varied histology. There are patches of fatty infiltration interposed with zones of "clear cells" and

"dark cells". Cellular cytolysis (homogenous atrophic degeneration), is observed in which the chondriome and the ribonucleins have disappeared. Bordering on these lesions, cellular regeneration is seen as nodules of little neoform parenchymatous cells, which are dark and rich in mitochondria and ribonucleins. The mesenchymatous reaction is very active. Fibrillar reticulosis with young cicatricial fibrosis is seen with proliferation of cells on the periphery of the hyperplastic nodules.

Essentially, the cirrhotic process is not yet mature. Significant features are the altered lobular structure due to abnormal regenerative nodulation and the start of the mesenchymatous scar. At this stage it is difficult to localize the portal space or the centrolobular vein of each lobule (Fig. 5).

Case 21:—Mrs. M. The various test results and findings in the case referred to in Figure 5 showed: Total protein, gm/100—7.2; albumin—4.05; globulin—3.15; A/G ratio—1.3.

Electrophoresis:—Albumin—49.1 per cent; globulin α1—1 per cent; globulin α2—4.7 per cent; globulin β—12.9 per cent and globulin γ—32.2 per cent.

Flocculation tests:—Maclagan (°BM)—35; Gros (c.c.)—1.3; Hanger—+++; Kunkel (°BM)—55; red colloidal—5.

	Ur	Gal	H.A.
2 hr.	260	1.65	3.04
4 hr.	250	0.89	
10 hr.	175		
24 hr.	650		
Total	1335	2.54	

Laboratory studies revealed functional changes in the six patients observed. The liver filtration tests were abnormal: polyuria, oliguria, increased galactosuria and decreased hippuricuria were all recorded. Most of the flocculation tests were abnormal (Gros, Maclagan and red colloidal reaction). On the other hand, the Kunkel reaction was normal. The fact that the Kunkel test was normal, differentiates the steatosic form.

Serum proteins were variable. Hypoalbuminemia and hyperglobulinemia were both present. Electrophoresis was studied in four patients. The gamma globulin was higher than the normal 15 per cent.

Steatosic cirrhogenous cirrhosis, even when it improves under the influence of lipotropic drugs, always terminates in cirrhosis. We have observed residual cirrhosis in one patient and incipient cirrhosis in three patients.

Cytolytic cirrhogenous hepatitis:—Cytolytic hepatitis differed from the steatosic form in that superfluous fat was absent. In addition, diffuse parenchymatous hepatitis was present. The "clear cells", when present, had generalized and homogenous protoplasmic atrophy, together with a pyknotic nucleus. On the other hand, nodular hyperplasia of the little, dark "regeneration" cells was observed. These were abnormally exaggerated groups which were not nodular since encircling fibrous septa had not yet appeared. There was a circumferential mesenchymal reaction, however, consisting of thick reticular fibers and of mononuclear cell infiltrations (Fig. 6).

Case 8:—Mrs. D. The case illustrated in Figure 6 presented the following: Total protein, gm./100—7.4; Albumin 2.7; globulin—4.7; A/G ratio—0.57.

Electrophoresis:—Albumin— —; globulin α and globulin β—+ and globulin γ—+++.

Flocculation tests:—Maclagan (°BM)—76; Gros (c.c.)—0.8; Hanger—+++; Kunkel (°BM)—110; red colloidal—5.

	Ur	Gal	H.A.
2 hr.	75	1.05	1.97
4 hr.	75	0.63	
10 hr.	75	0.34	
24 hr.	200		
Total	425	2.02	

Laboratory studies of hepatic function, as seen in the steatosic variety, revealed much disturbance. Hepatic filtration tests were abnormal. Flocculation tests were strongly positive (including Kunkel's). Accentuated disturbances in serum proteins and in their electrophoretic patterns were observed in all eight patients.

Liver filtration tests were abnormal in these cases. Abnormal hippuricuria were observed. The positive flocculation reactions in the eight patients were greater than in the steatosic form (Maclagan was from 45° to 100° B.M.; Gros was from 0.7 c.c. to 1 c.c.). The red colloidal reaction was regularly at 5. Finally, as opposed to the steatosic form, Kunkel's test was always strongly positive (from 64° to more than 100° B.M.).

In all cases, the quantitative serum albumin was diminished (from 2.50 to 3.50 gm. per cent). Electrophoresis revealed a drop in the albumin and an increase in the gamma globulins. These changes, in general, were greater than in the steatosic form. It was noted that the beta and gamma globulin were difficult to separate.

This form relentlessly develops in a slow, progressive fashion towards incipient cirrhosis and to the stage of later decompensated cirrhosis.

Incipient Cirrhosis (Biologically Decompensated) and Residual Cirrhosis (Biologically Compensated)

"Incipient" cirrhosis and "residual" cirrhosis are end-stages in the pathogenesis of alcoholic hepatitis. Histologically, the picture is that of annular cirrhosis.

This stage followed either a cytolytic cirrhogenous hepatitis or several recurrences of steatosic cirrhogenous hepatitis after the disappearance of super-

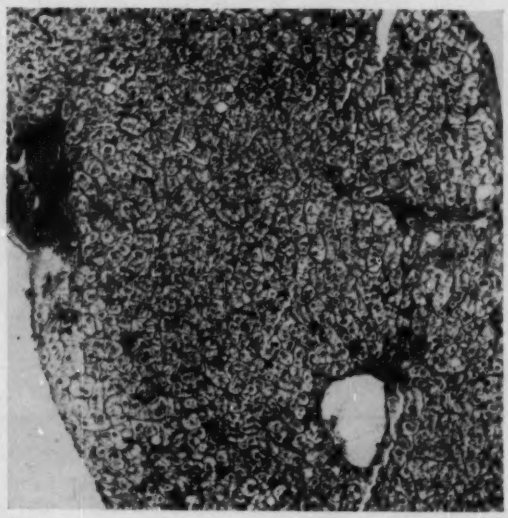

Fig. 3—(Case 31, Mr. Z.) The histobiological syndrome of subacute cytolytic hepatitis (Masson blue). Generalized "clearing" of cells plus neoform dark cells is seen histologically. Disturbance in hepatic infiltration plus normal flocculation tests are observed physiologically.

fluous fat. When the functional tests improved, even if partially, it was considered to be an "incipient" cirrhosis. This phase was clinically latent, but biologically decompensated. It was common.

Infrequently "residual" cirrhosis was observed. In this phase histological changes had been completely stabilized and hepatic function was adequate and compensated.

Incipient cirrhosis (annular cirrhosis—clinically latent and biologically compensated):—Clinically, there was found the dyspepsia of hepatic deficiency, irritability due to chronic alcoholic intoxication, weight loss and a sense of

pressure and fullness in the right hypochondrium. Physical examination revealed only hepatosplenomegaly. At this time portal hypertension was already increased to between 20 and 35 cm. of water (laparotomy at this time is dangerous because of bleeding from the large varices).

Laboratory tests were most important. These indicated that the apparently latent case of cirrhosis was biologically decompensated. The laboratory findings (biologic formula) were fairly characteristic. We have observed them in very many cases.

Hepatic filtration (passage tests) is disassociated. For example, if hippuric acid conjugation is decreased, galactosuria may be slightly increased and/or polyuria and proiuria (more urine after two hours than the 200 gm. of water that

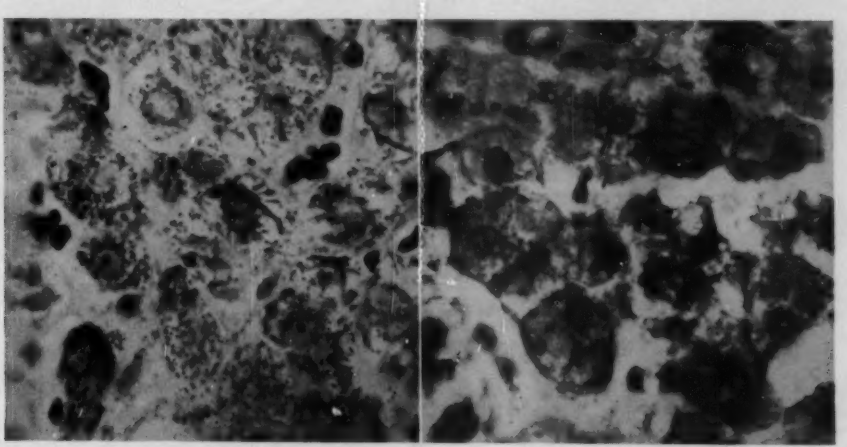

Fig. 4—(Case 31, Mr. Z.) Cytological details of subacute cytolytic hepatitis. *Right*, study of mitochondria (Regaud stain) showing the two types of cells: a. clear cells with sparse marginated chondriome and b. small, dark regeneration cells with abundant, compressed chondriome.
Left, study of ribonucleins (Pappenheim-Unna stain) showing the sparsity of ribonucleins in the clear cells and the great concentration (red) in the small, dark regeneration cells.

the patient has taken)are present. This polyuria persisted until the appearance of oliguria which prophesied several weeks in advance, the imminence of serious hepatic decompensation (icterus, ascites and coma)[3].

The flocculation tests were affected to varying degrees. The red colloidal reaction, however, was always strongly positive (4 or 5) and the bromsulfalein test showed much retention. These revealed the true state of the cirrhotic process.

There was also hyperglobulinemia. In addition, the electrophoretic pattern showed the predominance of the gamma globulins.

The evolution of this form was generally progressive; its duration was spread over a period of ten months to three years. Once established, incipient cirrhosis did not regress. Physiologic deficiencies may persist for months or years until the final cataclysm, represented by icterus and ascites, appeared.

Residual cirrhosis (annular cirrhosis, biologically compensated):—This rare variety was characterized by the fact that the tests of hepatic function were normal. There was usually found, however, serum hyperglobulinemia and, under electrophoresis, hypergammaglobulinemia.

This condition was observed after steatosic cirrhogenous hepatitis had been treated with lipotrophic medications and after cytolytic hepatitis had been treated by ligation of the hepatic artery.

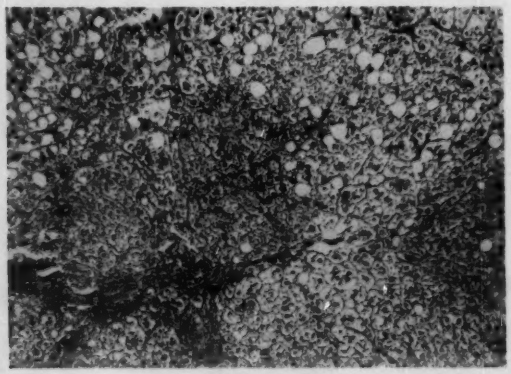

Fig. 5—(Case 21, Mrs. M.) The histobiological syndrome of steatosic cirrhogenous hepatitis (Masson blue). On the histological preparation, three types of lesions are seen: areas of steatosis, areas of clear cells and round areas of small neoform cells (small islands of nodular hyperplasia, representing the earliest phase of cirrhotic process). Biologically, widespread disorders appear in hepatic filtration and in the flocculation tests (except for the normal Kunkel).

Physiological compensation may be maintained for long intervals in these patients. As exacerbation of steatosic or cytolytic hepatitis was possible if intemperate habits are again resumed.

Evaluation and Comparison of Laboratory Findings

About 25 years ago Fiessinger and Walter used the term *instantané hépatique* (momentary hepatic status) to indicate that numerous synchronous studies were most valuable in determining liver function. Using this method of evaluating the "momentary hepatic status" we can differentiate the various types of alcoholic hepatitis.

The negativity of the flocculation tests (including the red colloidal reaction) contrasted with changes in hepatic filtration will exclude steatosic cirrhogenous hepatitis, cirrhogenous hepatitis and incipient cirrhosis, and will be diagnostic of subacute hepatitis.

A red colloidal reaction of 4 or 5, accompanied by widespread disorders affecting hepatic filtration and the flocculation tests, but with a normal Kunkel test, will point to steatosic cirrhogenous hepatitis.

The same formula, but more accentuated and accompanied by anomalies in the Kunkel test, is characteristic of cytolytic cirrhogenous hepatitis.

Another form of dissociation, characterized by a strong red colloidal reaction, some disturbances in flocculation tests, and in galactosuria and hippuri-

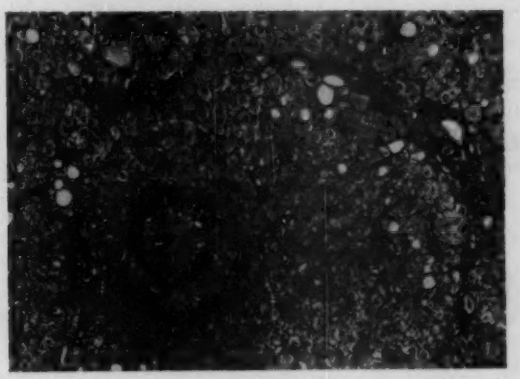

Fig. 6—(Case 8, Mrs. D.) Histobiological syndrome of cytolytic cirrhogenous hepatitis (Masson blue). Annular sclerosis is not observed. There are, however, nodules of cellular hyperplasia on which sclerosis may appear. Biologically, widespread disorders are observed in the passage filtration and in the flocculation tests (including the Kunkel test).

curia, together with normal or increased urine volume is typical of incipient cirrhosis (biologically decompensated).

Pathogenesis of Alcoholic Hepatitis

Each of the forms described above may have a separate pathogenesis. The prognosis is naturally more serious in cirrhogenous hepatitis which has already marked the hepatic parenchyma by alteration in the lobular structure.

Although it is difficult to observe this evolution in its entirety there is no doubt that these patients pass consecutively through the different stages of subacute hepatitis, cirrhogenous hepatitis and incipient cirrhosis[8,9,10,17].

Subacute cytolytic hepatitis may, following total abstinence from toxic agents together with correction of digestive disturbances (including vitamin therapy),

be relieved without biological or anatomical sequelae. We have not yet, however, observed this. On the other hand, repeated toxic episodes will be accompanied by the development of cytolytic cirrhogenous hepatitis.

Subacute steatosic hepatitis may improve during medical management, including total abstinence from toxic agents and the administration of vitamins and lipotropic agents. This improvement is often incomplete and affects only the surplus hepatic fat. A residual cytolytic hepatitis usually persists. In addition, in certain patients, in spite of treatment, the steatosic cirrhogenous hepatitis is seen to merge into actual cirrhosis.

The pathogenesis of cirrhogenous hepatitis differs in the cytolytic and steatosic types.

When cytolytic cirrhogenous hepatitis progresses to cirrhosis, the biological disturbances remain unmodified and neither aggravation nor remission are seen.

By contrast, steatosic cirrhogenous hepatitis may present rec rences which lipotropic therapy (especially Santenoise's vagotinine) shortens. Without therapy serious mutilating annular cirrhosis will develop. The most to be expected from intensive medical therapy, even if successful, is an "incipient" or "residual" cirrhosis.

Residual cirrhosis is a transient phase of months' or years' duration. It, too, has recurrences and exacerbations[25]. In the presence of additional intoxication or intercurrent infections, these exacerbations may resemble any of the forms of precirrhosis which have been described. We were even able to observe in one patient the rare appearance of subacute steatosic hepatitis. This patient had recovered from cirrhogenous steatosic hepatitis and showed a residual cirrhosis. The attack of noncirrhogenous steatosic hepatitis was relieved by lipotropic medical treatment without the symptoms of evolutive cirrhogenous hepatitis reappearing.

Incipient cirrhosis with biological decompensation is now no longer included in the category of precirrhosis. It develops progressively over several months, towards an accentuation of the cirrhotic process. The evolutive waves of cytolytic cirrhosis or steatosic cirrhosis which occur are foreshadowed by the disappearance of proiuria and the appearance of opsiuria.

Conclusions

The "momentary hepatic status" and needle biopsy of the liver permit the differential diagnosis of various histobiological forms of alcoholic hepatitis.

Subacute hepatitis may occur in two types: 1. the "steatosic" form complicated by surplus fat and 2. the "cytolytic" form wherein diffuse parenchymatous hepatitis is characterized by "clear" hepatic cells. These two types are identified by disturbances in hepatic filtration (diuresis, galactosuria, hippuri-

curia) and by the normal flocculation reactions, notably of the red colloidal reaction.

Alcoholic precirrhosis may occur in two forms: 1. steatosic cirrhogenous hepatitis and 2. cytolytic cirrhogenous hepatitis. These are differentiated by the Kunkel test which is normal in steatosic cirrhogenous hepatitis. These are both differentiated from subacute hepatitis by the positive flocculation reactions (especially of the red colloidal reaction).

Cirrhosis develops from either of these forms. Bands of cytolytic atrophy are replaced by nodules of compensating hyperplasia around which annular sclerosis develops. Steatosis is an additional feature which plays an auxiliary role in the genesis of cirrhosis.

Steatosic cirrhogenous hepatitis, however, is characterized by relief following lipotropic medical treatment. In addition, its development is in the form of periodic exacerbations, whereas cytolytic cirrhogenous hepatitis develops continuously over a long period.

Residual cirrhosis, with a return to normal hepatic functional tests, is rare. It may be observed in the steatosic form.

Incipient cirrhosis, which is clinically compensated, is already biologically decompensated. This is observed by evaluation of liver function with special attention to the "momentary hepatic status". In incipient cirrhosis there is galactosuria, proiuria, variable anomalies in the flocculation tests and a strong red colloidal reaction. The disappearance of proiuria and the presence of opsiuria will announce, (after long months of apparently stable evolution, and several weeks in advance) the imminence of complete hepatic decompensation (icterus, ascites, etc.).

Where it is possible to follow the entire course of a patient with cirrhosis from beginning to end of the affection, each change in liver histology denoting the passage from one form to another is accompanied by parallel changes in the hepatic physiology. The value of tests for liver function is thereby further substantiated.

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RECTAL SUPPOSITORY MEDICATION VERSUS THE ORAL OR PARENTERAL ROUTE

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Some medical historians suggest that prehistoric man may have perceived the concept of rectal medication from watching the stork scoop water into its elongated bill and, by means of its pipe-like neck, instill the water into its cloaca. History is mute on the discovery of suppositories, but there is indisputable evidence that they were known and used at least 4,000 years ago[1].

The Ebers Papyrus, which scholars date circa 1550 B.C., contained the codified medicine and pharmacopeia of the Egyptians of 3,500 years ago. Listed are over 700 drugs, botanical and mineral, representing perhaps several hundred years of prior empirical experience. Among the 800-odd formulations included in the Ebers Papyrus were suppositories for laxation and for relief from hemorrhoids. These suppositories consisted of conical chips of wood or bone, about the size of the little finger, which were rolled in cooked honey containing the medicament. Upon defecation, these shaped chips were retrieved, washed and then reused as needed. This type of suppository "base" was utilized up to the 16th century, but instead of wood or bone, "disposable" bases cut from beets, cabbage hearts and tuberous roots were employed.

Perhaps the first mention of a suppository for systemic effect is contained in the writings of Hippocrates (460-370 B.C.) who listed what was probably an antiasthmatic formula "to improve the breathing of young children". It was composed of anise, myrrh, goosegrease and honey. He also listed a laxative suppository containing bile salts and a hemorrhoidal suppository containing alum and gallates. Hippocrates has used the Greek word for "gland" to describe suppositories, ostensibly because of the considered similarity in shape. The word "suppositorium" (now suppository) was born sometime in the 17th century. It stems from the Latin verb *supponere*—to substitute for, and probably arose when laxative suppositories were used as substitutes for enemas.

The development of the soap suppository for purposes of laxation, circa 1650 A.D., was an invention claimed for their respective countries by French, German and English medical historians[2]. These soap suppositories were considered more gentle in action and were designed to accommodate patients who could no longer tolerate the exhausting series of enemas, lavages and compound clysteres then in therapuetic vogue. A century after the invention of the soap suppository came the advent of cocoa butter, mentioned as an additive to honey, waxes and greases for the suppository bases in the pharmacopeias circa 1760. By then, the analgesic suppository of opium had come into being. Development

of the rectal route of administration for systemic effect, however, was hindered by the natural reaction of the medical profession to the abusively excessive indulgence in the use of laxative suppositories by the public.

The neglect of the rectal route was in turn checked by the interest of physicians, during the decades 1840-1860, in putting to better use some of the botanically-derived therapeutic principles (such as atropine) which were isolated and identified at about that time. By now, cocoa butter was, despite its variability, the suppository base of choice. The thought that water-soluble medicaments might be better employed in a water-soluble suppository base led to the development of glycerinated gelatine mixtures circa 1875. It is interesting to note that pharmacopeias of the day called for 5 gm. suppositories. The years since then have seen a steady reduction in size to the 2 gm. suppository popular today.

The first quarter of the 20th century saw such a rapid development of new therapeutic agents from the flowering of organic chemistry in Germany, France and England that preoccupation with their use orally, and by the then newly-improved technics of hypodermic injection, over-shadowed interest in rectal applications. This is the era that gave rise to the prototype analgesic, antipyretic, sedative, hypnotic, spasmolytic, sympathomimetic and bactericidal preparations in use today. Strides in immunology also focussed attention on vaccines and serums parenterally administered to combat infectious diseases.

When, however, the novelty of these developments wore off in the 1930's, and some of the disadvantages inherent in the oral use of the new drugs came to light, interest, principally in Europe, was once more directed to the rectal route of administration. For example, Ravaud[3] in 1935 reported that alkaloids (atropine) purines and xanthines are more rapidly effective by rectum than by mouth and require smaller doses for equivalent effect; that barbiturates and antipyretics are about equally effective by rectum as by mouth.

Because the rectal route of administration by-passes the palate, the stomach, and, for the most part, the hepatic circulation, the use of suppositories appears as a rational way of avoiding gastric upset while effecting a systemic response to certain drugs. In gastroenterological cases involving dyspepsia, gastritis, peptic ulcer and the "irritable gallbladder syndrome", where symptoms include nausea and vomiting, we could hope to find particular advantage in the suppository as against pills, capsules or liquids, *per os*.

Self-medication will always be indulged in by the laity. Severe nausea and vomiting frequently accompanied by pain, however, cause many to seek medical assistance. Some requirements of drugs used in gastroenterology would include: 1. Ease of administration, 2. speed of action, 3. a definite therapeutic dosage level. Since emesis of medication, both liquid or solid may commonly occur we

may not be able to accurately satisfy the 3 points enumerated, via the oral route; if precipitation occurs in the syringe because of incompatability of drugs, multiple injections may be necessary. Finally, all of us have seen the patient who is "needle-shy" refusing adamantly to accept a hypodermic. Suppository may then be the choice.

Many workers have reported a synergistic action when belladonna or its derivatives are combined with barbiturates. Using a proprietary suppository which contained the levorotatory alkaloids of belladonna 0.50 mg. with 90 mg. of phenobarbital in a cocoa butter base, satisfactory results were obtained by us in cases of gallbladder spasm associated with vomiting, and in pain due to peptic ulcer. We were impressed, however, with a degree of tardiness in onset of action. Therefore, retaining the levorotatory alkaloids of belladonna we began to substitute the more rapidly acting barbiturates such as secobarbital and pentobarbital 90 mg. A material improvement was noted, with suppression and alleviation of symptoms occurring within 35-40 minutes, particularly nausea, retching and spasm. Alternating dosages; we observed 21 cases noting good to excellent results within 30 minutes to 1 hour. There were practically no remarkable differences or side-effects noted with these 2 suppository formulas.

Total levorotatory alkaloids of belladonna: TLAB

1. TLAB 0.50 mg.
   Secobarbital 90 mg.
   ol. Theobrom qs.

2. Extract of Belladonna 10 mg.
   Secobarbital 90 mg.
   ol. Theobrom qs.

Relief was somewhat slower, but also effective with:

Dicyclomine hydrochloride* 20 mg.

Secobarbital 90 mg.

ol. Theobrom qs.

This formula was used when belladonna or its compounds were contraindicated due to age of patient or history of increased intraocular pressure.

(Pharmacologically the belladonna and barbiturates are incompatible in the hypodermic syringe.)

This suppository combination has been put to prophylactic use by patients at home. Recurrent gallbladder attacks both calculus and noncalculus were controlled with good to excellent results. They employed this type of suppository early at the onset of symptoms (within the first 30 minutes to an hour) when the prodromal signs appeared: pressing beneath the right margin of the sternum

*Bentyl.

or rib cage, right shoulder pain or pressure, epigastric fullness, slight nausea, heartburn and eructation.

Case 1:—S. L., C-7446, female, 48 years old, housewife, 6 children. Past History: Heartburn, gas. 1946—complained of RUQ pains. Physical examination revealed an obese female with tenderness of the gallbladder. X-ray findings were negative. During the following 4 years patient developed intermittent attacks of dyspepsia usually accompanied by pain in right shoulder and beneath right rib cage. Weight rose to over 200 pounds, and symptoms persisted. The pattern was usually the same, onset would be preceded by dietary indiscretion, or emotional upset. Symptoms would be severe by midnight, necessitating a house-call with administration of an opiate and an antispasmodic, sometimes followed by increased vomiting. Average duration of attacks 5-7 hours. October 18, 1954 patient had early symptoms. A suppository containing TLAB 50 mg., phenobarbital 90 mg. in cocoa-butter base was used. Relief was obtained in 45 minutes. Patient was then placed on powder containing aluminum hydroxide 0.3 gm., extract belladonna 10 mg., phenobarbital 15 mg. taken 2-3 times daily. Patient was never symptom-free for too long a period of time. Re-x-rays of the gallbladder were done January 13, 1955. No stones, only a poorly functioning gallbladder was noted. Dehydrocholic acid gr. II extract of belladonna 10 mg. were prescribed, twice daily. Results were equivocal. May 1955 severe attack, vomiting, pain, required hypodermic. Patient was given a suppository containing TLAB 50 mg., secobarbital 90 mg. to be kept in readiness whenever symptoms occurred to be used rectally—nothing by mouth.

Results:—Twelve months, no actual attacks or spasm. Relief promptly in minutes. March 9, 1956. Patient was re-x-rayed. Noncalculus gallbladder which showed delayed emptying time. Biliary dyskinesia noted.

Present day research and development in suppository therapy are particularly directed toward regulating the rate and extent of absorption from the rectal mucosa. In the past it was thought, erroneously that the nature of the base was not too important because water soluble medicaments would be absorbed into lymph. Left unanswered were questions concerning such anomalies as the lack of absorption of strophanthin as against the solubility of its close chemical relative, digitalis.

Peterson, Lee and Christian[4] (1953), Cacchillo and Hassler[5] (1954), Peterson and Guida[6] (1953), all noted that the physicochemical characteristics of a suppository base greatly affected the rate and extent of absorption of the medicament it contains. Further, each choice of a suppository base must be made on the basis of experimental work, since considerable latitude is apparently available in the release time of the therapeutic agent. Recent reports in the literature have brought out the value of controlled slowly released medication in tablet or capsule form. Application of this has been made in gastroenterology for spasm, sedation, hypersecretion of peptic ulcer and antihistamine therapy in

allergy. We are greatly interested in using the controlled melting point base and utilizing this unique feature in suppository form. Cacchillo and Hassler's preliminary studies found that if blood levels at a given interval following oral administration of 10 grains of acetylsalicylic acid are assigned an arbitrary value of 100, a Carbowax-based suppository containing the same amount of drug would have an absorption index of 93; cocoa butter-based suppositories would have an index of 66; glycerated gelatin-based suppositories would have an index of 53, all after the same interval.

Peterson, Lee and Christian, using sodium iodide made from radioactive iodine isotope (I^{131}), showed that after 30 minutes about 10 per cent of the material was absorbed into the bloodstream of mice from a cocoa butter suppository. Forty-five per cent was absorbed from a "Tween 61" based suppository and 75 per cent from a glycerated gelatin-based suppository. At the end of two hours, the absorption was 40 per cent, 60 per cent and 95 per cent, respectively. The effect of variations in melting point of the suppository bases used was not taken into consideration for the purposes of this experiment. The tendency of past practice has been to merely make certain that the base melts at body temperature or slightly below it. Preliminary work is now in progress by us with a suppository base which has a wide range of melting points controlled $\pm$ 1° F*. It is claimed that this new base can have its melting time adjusted from a low of 10 minutes to as much as 12 hours, making possible rapid onset of therapeutic effect with prolonged action, if desired. As further studies are completed they will be presented in the pages of this journal.

Application of the findings of these experiments and the as yet unpublished work conducted by some of the pharmaceutical houses may greatly enhance the usefulness of the rectal route of administration of medicaments. Nothing definite has yet been reported on attempts made to temporarily alter the local physiology and chemistry of the rectal mucosa to permit the controlled absorption of therapeutic agents heretofore not useful in suppository form. These developments may provide the clinician with new therapeutic preparations that have numerous advantages over those currently in use.

Apart from these newer possibilities, rectal administration affords the clinician an alternate route to simplify the regimen of patients requiring several oral preparations to be taken concomitantly. This would probably improve the patients' attitude by not taxing his cooperation in taking pills. Further, the recent availability of sanitary, single-use, disposable applicators for suppositories overcomes, from the patient's point of view, one of the principal objections to this form of therapy.

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*Prepared by the makers of Anatoid, for whose help in the preparation of the historical information here presented we are also indebted.

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DIABETES MELLITUS IN THE TEXTS OF OLD HINDU MEDICINE (CHARAKA, SUSRUTA, VAGBHATA)

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Before considering anything else, it seems indispensable to define the term "Old Hindu Medicine" on the basis of present day knowledge. Any attempt to do this encompasses the people concerned no less than the time of their achievements.

Historical Introduction

A. The People:—Who were those old Hindus? This is already a rather controversial question, by no means conclusively answered. The theory that they were not the aborigines of India but Aryan tribes who invaded and conquered the country at about 1500 B.C., and later on migrated to the West, was based by its inventors upon the debatable evidence of the affinity of a certain number of words in the Sanskrit language with those of many ancient and modern languages of Europe and Asia. The main source of such speculations, conceived first by Coeurdoux (1767) and Sir William Jones (1786), and elaborated later by Friedrich Schlegel, Max Mueller and many others, were the *Vedas* (*Veda* = Knowledge). They consist of three groupings of still earlier *Mantra*–material (*Mantra* = Prayers) and are called *Rig Veda, Sama V., Yajur V.;* a fourth grouping (*Atharva V.*) is said to be the oldest literary monument of medicine in history (G. N. Mukerjee, 1913) and mentions herbs as remedies against a number of diseases and injuries (R. K. Mookerji, 1951). The genuineness of the *Atharva V.* is, however, not accepted by all (M. Bloomfield, 1897) and it was for a long time not regarded as canonical. The *Vedas* form the body of religious doctrine for the Hindus who believe that these scriptures represent the oldest writing on earth (B. S. Jee, 1927). They derive their name from the opinion that all knowledge has its sources in the *Vedas*; they are asserted to be of *Aryan* origin by many modern Indian and Western authors. These authors contend that the *Vedas* were brought to India by the Aryans when they invaded India from the North. Quite recent linguistic studies, however, have revealed the use, in the *Vedas,* of many medical words and terms which have their origin in pre-Aryan languages (W. Kirfel, 1955).

The physical features of the Aryan people are described in the *Vedas* and their culture has been colorfully painted in detail by modern writers (H. G. Wells, 1926). There is, however, no record at all of Aryan settlements in India (R. C. Dutt, 1917), and nobody ever saw any palpable proof of their actual existence. In view of the fact that "concrete evidence of the Aryans in India has yet to be found" (St. Piggott, 1945) the Aryan theory with its cultural and racial inferences has become more and more doubted and, by some, even re-

jected (B. S. Jee, 1927). Moreover, the belief in the invading Aryans as "the torchbearers of civilization and culture" has been undermined in the last few decades by archaeological findings which prove that a highly developed autochthonous civilization flourished in the great cities (Mohenjo-Daro, Marappa etc.) inhabited by a pre-Aryan people, the *Dasus* (V. G. Childe, 1952; R. H. Major, 1954; D. Ch. Muthu, 1930). They had a written script and an imperial organization at about 2400 B.C.; but "their Empire collapsed about 1500 B.C. and we don't know how" (St. Piggott, 1945). If they actually were overrun by invading Aryan tribes the latter may just as well be called "barbarian hordes who destroyed the high civilization of the Dasus" (V. G. Childe, 1952).

The most cautious statement we can possibly make as to the people who created the Hindu culture and science is the admission that everything concerning them is "shrouded in antiquity" and almost nothing can be said with certainty.

B. The Time:—It is equally difficult to determine exactly the time when Hindu culture originated, developed and flourished. There is no way to fix the date of the Vedic scriptures (R. F. G. Mueller, 1932) although it is generally assumed that they came into existence in the period between 1500 B.C. (or even earlier) and 600 B.C. While we may accept the teaching that the *Vedas* contained "traces of medical science", we are at a complete loss about the time of origin of what is now called *Ayur Veda*. It is purely legendary and is said to have contained all branches of medicine in eight different sections. The name *Ayur Veda* stands now for the ancient Indian medical tradition which in its earliest beginnings may be traced back to the old Vedic scriptures but, later on, became codified in comprehensive textbooks. The latter, again according to legend, drew their inspiration and wisdom from Brahma himself. The most important of these textbooks or *Samhitas* bear the names of three outstanding physicians (Charaka, Susruta, Vagbhata), the so-called *Holy Triad* (*Vrddha Trayi*).

With regard to timing much useful information was gained from the so-called "Bower Manuscript" which was found incidentally in 1890, has been translated by Hoernle and is now stored in the Bodleian Library, Oxford. It was written in the 5th cent. A. D. (I. Bloch, 1902; J. Jolly, 1901; R. Hoernle, 1906-09; R. Hoernle, 1907), refers to the compendium of Susruta (Su) and mentions diabetes. It is the earliest medical manuscript of India so far known. Although it does not mention Charaka (Cha) by name, its text shows more and closer parallels with him than with Su.

C. The Authors:—Discussing Cha, Su and Vagbhata (Va), we already encounter the difficulty that, due to the lack of preservation of any original texts, we do not know for certain who they were and at what time they actually lived. Neither do we know whether any of the books, named after their respective authors, were written by one or two or more physicians.

1. Charaka (Cha):—This author is generally believed to be the oldest of the three (G. N. Mukerjee, 1923-29). According to legend he was a pupil of Agnivesa who had acquired medical knowledge through Atreya Punarvasu from Brahma himself. An instructive table of the legendary history of Cha's work is given by J. Filliozat (1949).

Indian lore places Cha, and also Su, into the so-called "Epic Period", 2500–600 B.C. (Muthu, 1930). Plausible studies (J. Jolly, 1901; Major, 1954) now place Cha in the time of Kaniska, King of Cashmere, who reigned in the 1st century either B.C. or A.D. There may have been an earlier text, ascribed to Cha and written in the 6th cent. B.C. (Hoernle, 1906-1909; Hoernle, 1907); if it ever existed, it has been lost. What we really have now are corrections and additions of later writers, the most important of whom is Drdhavala who lived in the 8th cent. A.D. (Hoernle, 1908) and added whole sections to the book of Cha as it existed at his time.

Cha's *Samhita* (Sam) is a vast repository of a variety of important subjects (K. N. Gupta, 1909); it is mostly concerned with internal medicine. Cha was an excellent, far-seeing, ethical physician who is quoted as saying that "those who sell the treatment of disease as merchandise gather the dust and neglect the gold" (B. L. Gordon, 1949).

2. Susruta (Su):—Su's name is first referred to in the Bower Manuscript. His actual life time is as uncertain as that of Cha, and the different opinions range from 1000 B.C. (A. Castiglioni, 1947) to the 7th cent. A.D. (Mueller, 1942). The *Su Sam* in its original, no longer existing, form is like the *Cha Sam* believed in India to be divine in origin (Bloch, 1902). What is still extant is probably the work of an author who is now called Su II (Gordon, 1949). He supplemented the original treatise by adding the *Uttara Tantra* (that is: supplementary chapters) and at the same time revised it. Su II is said to have taught medicine, and particularly surgery, at the university of Benares, the holy city of India (Major, 1954). The final revision, according to tradition, was prepared by the Buddhist Nagarjuna at about 100 A.D. (Jolly, 1901). Another opinion is that the book that goes under Su's name was compiled about 500 A.D. (P. Diepgen, 1949). Again others believe that the *Su Sam* owes its present form to the commentator Dallhanacarya who probably lived in the 11th cent. A.D. (P. Cordier, 1896).

3. Vagbhata (Va):—Our knowledge of the life of Va is somewhat better established. We may assume that he lived in the 7th cent. A.D. (Hoernle, 1908; Mueller, 1932). He based his *Sam* upon the writings of Cha, Su, and others before him.

Besides the work attributed to Va himself, the so-called *Vrddha Va, (Astanga Samgraha, As),* there exists another work *(Astanga Hrdaya, Ah)* which is ascribed to a writer of the 9th cent. A.D. to whom customarily the name Va II (Pseudo-Va) is given. Ah is supposed to be the most systematic and com-

prehensive work of all Samhitas still existing. Both versions may be nothing else than two revisions of the same original text the exact date and contents of which are unknown. They both show remarkable similarities with the *Cha Sam.*

In summarizing the opinions of the most competent sanskritists we may assume that the textbooks of the Holy Triad originated in the time between 100 B.C. and 700 A.D.

4. Other Authors:—Apart from Cha, Su and Va, there were numerous others; some of them important, some mere copyists (Bloch, 1902). To name but a few: Madhava who wrote a valuable book on pathology in the 8th cent. A.D.; Cakrapani Datta who lived in the 11th cent. A.D. and wrote a companion volume to Madhava's work, still in high esteem in India. There is also the medical encyclopedist Bhavamisra who flourished in the 16th cent. A.D. and was the first to describe syphilis, the *Portuguese disease.*

It should be mentioned here that of all the successive periods in the history of Indian medicine (conf. Muthu, 1930) the Buddhist period (4th century B.C. to 8th century A.D.) was its "Golden Age" (Gordon, 1949). Only a few names of Buddhist medical writers can be given here: Nagarjuna (see above); Buddhadasa, King of Ceylon in the 4th cent. A.D.; Buddha Bhaisajya Guru, the "master of medicaments".

An extensive list of most of the later medical authors is given by Jolly (1901) and by Hoernle (1907).

D. Translations:—All the *Ayur Vedic* texts are written in Sanskrit; the most important ones are translated and printed in one or more of the many oriental languages like Bengali, Telugu, Tibetan, etc. None of these languages, Sanskrit included, is understood by the average Western physician, not counting a few rare exceptions. There exist, however, translations of *Cha Sam* by A. Ch. Kaviratna, and of *Su Sam* by K. K. L. Bishagratna, both into English; and of *Va Sam* (Ah) by Hilgenberg and W. Kirfel, into German. These translations are generally accepted as reliable, and were consequently perused for our purpose.

Leaving the final answer to the meaning of obscure passages to the learned and often quite subtle interpretations of Sanskrit scholars, European and Asian alike, we feel that an essay as presented here is nevertheless justified. There is, after all, no other way for the physician, historically minded but not acquainted with Sanskrit, to have his interest in old Hindu medicine stimulated, and, particularly, to learn something about the early history of diabetes mellitus.

Diseased Flow of Urine (Prameha)

Prameha is the term used in the classical textbooks for "diseased flow of urine". Meha literally means "to micturate". It would be wrong to translate *Prameha* with glycosuria; the latter is called *Iksumeha* (Sugar urine), or *Madhumeha* (Honey urine). We find in the texts themselves, however, *Prameha*

being used synonymously with *Madhumeha.* Va goes so far as to assert that "all varieties of *Prameha,* if neglected, will change to *Madhumeha* eventually because of the natural sweetness of the body".

When we compare the knowledge about diabetes in the old Indian textbooks with that of Greco-Roman medicine, it has to be stated that Hippocrates (460-377 B.C.) did not even mention the disease or any of its symptoms. It is true that Aretaeus of Cappadocia (b. 30 A.D.) already coined the term "diabetes" without however knowing the disease in its characteristic qualities (J. H. Barach, 1928). Not one author of the Greco-Roman school of the same and subsequent periods seems to have been acquainted with the sweet taste of urine (A. Hirsch, 1885) in certain patients; and all regarded the symptoms of what they called diabetes as caused by disease of the kidneys (Galen, Cornelius Celsus, Aetius of Amida) or of the stomach (Aretaeus of Cappodocia). The Arabian schools of later periods knew no more than what they had learned from translations of the old Indian texts.

Not until 1679 (Willis in England) was attention called again to the sweet taste of urine in certain patients, and in 1776 Dobson in England was the first to demonstrate that the sweet taste depended on a sugary substance which he detected by means of fermentation (Mueller, 1932). The first classical essay on diabetes mellitus was written by Rollo in 1796.

The observation of Willis had already been made 1,000 years or more before him by the Indian physicians. That it was subsequently forgotten can only be explained by the dominating influence of Galen upon European medicine. "It is a curious circumstance that the Indian physicians should have described so distinctly the sweetness of the urine which had escaped the observation of both the ancient and modern physicians of Europe till the time of Willis" (Th. Christie, 1811).

Prameha in the Textbooks

In the *Cha Sam, Prameha* and its complications are discussed in the sixth chapter of the *Cikitsa Sthana* (chapter of treatment of morbid urinary secretions and diabetes) in Kaviradna's translation Vol. 2, pp. 1194-1206, and in the sixteenth chapter of the *Sutra Sthana* (Diseases in general), l.c., pp. 194-200.

The *Su Sam* deals with *Prameha* in chapters 6 and 9 of its *Nidana Sthana* (discourse about causes and symptoms of diseases), Vol. 2 in Bhishagratna's translation, pp. 43-49, and in Chapters 11, 12 and 13 of its *Cikitsa Sthana,* l.c., pp. 372-391.

In the *Astangahridaya* (Ah) *Sam* of Va, the use of which has now superseded that of *Astangasamgraha* (As) and in certain parts of India that of all the other textbooks, we find the general discussion of *Prameha* in the 9th, 10th and 11th chapter of its *Nidana Sthana* in Hilgenberg and Kirfel's translation,

pp. 245 ff.; the therapy of *Prameha* and of its complications in the 12th and 13th chapter of its *Cikitsa Sthana*, l.c., pp. 404 ff.

Classification of Prameha

Prameha is divided into 20 varieties by Cha, Su and Va alike. The authors also agree with each other as to the three groups into which the 20 varieties are to be subdivided, according to the physiological factors causing and determining them. Ten of the varieties are said to be caused by "phlegm" *(Kapha, Kaphaja)*, six by "bile" *(Pitta, Pittaja)*, and four by "wind" *(Vataja, Vayu)*. These terms play the fundamental part in Hindu physiology and need brief discussion.

Physiology of Prameha in Hindu Medicine

Phlegm, bile and wind are called the three elements *(Dosha)*. They regulate the normal functions of all organs of the body. The role attributed to them, and the way they act, are difficult for the Western mind to understand. They probably are based upon very old ideas, found in the *Rig Veda*, and correspond to what is called therein *Tridhatu* (the three elements).

The basic theory is that all vessels converge in the region of the navel to which they bring not only blood but also phlegm, bile and wind. These four constituents flow through the whole body; if their harmonious flow is for some reason interfered with, disease ensues. Uncleanliness, bad climatic conditions, psychic disturbances are other causes of disease.

Bishagratna in his introduction to *Su Sam* interprets, like others (e.g. K. G. Sen, 1916), *Kapha* (phlegm) with "combustion" that goes on in the human system, *Pitta* (bile) with metabolism and the body heat derived from it, *Vayu* (wind) with "the nerve-force, which includes every kind of electromotor or molecular force". These principles are supposed to sustain life and health of the organism but may become transformed into the dynamics of disease, and be then the "vitiating elements".

There exists a fourth, even more enigmatic principle which is called *Ojah-Dhatu* and is explained by Bishagratna as "the refuse which forms under the influence of *Pitta* out of lymph or chyle, and then is passed off as excretion through the apertures of the body". In diseases caused by defective assimilation it is said to be ejected through the kidneys and to leave the body with the urine "as in certain types of *Prameha*, whereby the patient gradually loses strength, flesh, and healthy glow of complexion". Cha continues "When in lazy, gluttinous people the free course of urine is stopped, the latter seizes the *Ojas* and proceeds to the anal canal whereby a particularly painful form of diabetes is created".

We do not get much help for the interpretation of the *Ojas* from the Sanskritists. We find it designated as the sweet *Kraftstoff* (Mueller, 1932 and 1942)

which is forced by the wind into the urine with the result that *Madhumeha* ensues. Some believe that Ojas must be something of the nature of sugar and comes nearest to our "glycogen"; others identify it with phlegm that becomes a sort of evil and leads to disease when its normal condition is altered; Bishagratna (l.c., introduction) thinks that *Ojah* most likely means albumin. Again, *Ojah* is translated by *lecithin* (C. Chakraberty, 1923); it is regarded as "the impurity of the semen" (M. Datta, 1899); and it is also interpreted as physiological product of the semen that circulates in the body as an essential factor of metabolism (Br, Seal, 1915).

The Western orientalists are accused by some of their Oriental colleagues of having misunderstood, and wrongly translated, not only the word *Ojah* but also the terms *Kapha, Pitta* and *Vayu*. The modern Pandits assert that the true sense of Sanskrit with its often symbolical, frequently obscure meanings is hard to grasp by the occidental mind and particularly so when profound knowledge of Sanskrit is lacking. There may be some truth in this assertion. Those physiological terms and conceptions, however, remain highly artificial just the same, and very often unintelligible to the Western mind.

Diabetes Within the Varieties of Prameha

A. Charaka-Samhita:—Of the ten varieties of phlegm-born *Prameha,* the second interests us most. The urine in this variety looks like "the expressed juice of the sugar cane" and the condition, therefore, is given by Cha the name *Iksumeha* (sugar cane urine).

None of the six varieties of the bile-born *Prameha* is brought into connection with diabetes.

Of the four wind-born varieties the second is the condition where the urine is "mixed with *Ojas*" and called "*Madhumeha*" (honey urine).

Cha mentions the ingenious and often quoted observation that ants are attracted by the urine of persons afflicted with one of the two varieties characterized by sweetness of the urine.

B. Susruta-Samhita:—Iksumeha is here also listed as one of the ten phlegm-born *Mehas.* To the wind-born variety which is analogous to Cha's *Madhumeha,* Su gives the name *Kshaudrameha;* this means that the urine looks like honey and acquires a sweet taste.

Su also records the fact that the urine in cases of *Iksumeha* is assailed by flies.

Although the clinical description of the *Pittaja*-types by Su bears no connection with diabetes mellitus, Su stresses the fact that excessive thirst harasses the patient who suffers from any one of the *Mehas* of the *Pittaja*-types.

The *Vayu*-types, including *Kshaudrameha* are defined by Su in a quite unspecific way, except for the statement that patients suffering from them are "longing for food of all tastes".

C. Vagbhata (Ah):–As in Cha's text we find here among the 20 varieties of *Prameha* the *Iksumeha* and the *Madhumeha*. The Ah abandons the rigid grouping of the 20 varieties into three main groups formed by the specifically damaging influence of one of the three *Doshas*. It classifies the 20 varieties according to qualities of the urine, such as color, taste, odor, sediment, etc. Va, however, also differentiates the clinical symptoms in correlation with the specifically responsible *Dosha*. Consequently, *Madhumeha* is said by Va to originate from either one of two causes: "Either the wind gets excited subsequent to dwindling of the tissues, or it does not find anymore its correct way on account of the *Doshas* which obstruct its passage".

While Va to some degree still adheres to the *Dosha* theory, he brings the new idea that all the different varieties of *Prameha* may become *Madhumeha* in the course of time and in case of neglect.

The Clinical Features of Diabetes as Found in the Writings of Cha, Su and Va

1. Incidence:–No information about the frequency of diabetes is given by the old writers. We know from more recent sources that diabetes mellitus is frequent among rich, indolent, obese, elderly natives in Calcutta (A. Hirsch, 1885; N. Chevers, 1886). Another report found diabetes to be frequent in Ceylon but rare in Calcutta (Christie, 1811). Since these statements are contradictory they are not very useful when we attempt to assess the frequency of diabetes in old India by analogy. We must, however, not be too critical in this respect when we remember that "diabetes escaped the notice of physicians in all parts of the world for lack of their special training, the economical status of the masses, and the unawareness of its potential frequency" (Hirsch, 1885). This statement, made 70 years ago, applies even more to the remote past than to the time when it was made. Improvement of the situation is only now in its beginnings.

There is some reason to believe that diabetes was not too rare in old India, or else we could not explain why those old physicians dedicated whole chapters of their textbooks to its discussion.

Why diabetes should be common in countries like Ceylon and at least some parts of India where the people live exclusively on vegetables, while it is said to be infrequent in other parts of the world, where the population lives on the same diet, is not fully understood as yet. The modern concept of heredity of diabetes, which is in accordance with the Mendelian laws, is probably one of the explanations for this puzzling fact. We shall soon see that old Hindu medi-

cine already had some notion, though purely empirical, of the importance of heredity.

2. *Sex:*—Nothing is said in any of the textbooks about the distribution of *Prameha* between the sexes. The term *Samaroga* which is synonymous with *Madhumeha* is only mentioned in later books, where it is classified as another variety of *Prameha* peculiar to women and perhaps mistaken for leukorrhea (T. A. Wise, 1845).

3. *Etiology:—a. Congenital:*—About heredity of diabetes we find a passage in the *Cikitsa Sthana* of Cha which runs as follows: "A person suffering from congenital *Prameha* owing to the fact of his birth from a father afflicted with *Madhumeha* cannot be cured for the primary defect in the seed". Su also knew of the possibility of inheriting the disease. In chapter 11 of his *Cikitsa Sthana* he ascribed *Prameha* to two causes of which one is congenital defectiveness *(Sahaja)*, the other indulgence in injudicious food. *Sahaja* is said by Su to be due "to a defect in the seeds of one's parents" (Jolly, 1901).

Va does not mention the possibility of inheriting the disease.

b. Acquired:—1.) Diabetes as sequel of obesity:—In the introduction to a book on treatment of diabetes (F. M. Allen et al, 1919) we find the following statement: "The most prominent clinical feature and one of the most vitally supported hypotheses concerning the etiology of diabetes received their first mention in India." This obviously means acknowledgement of the old Indian physicians' acquaintance with glycosuria as well as with the mutual relation between obesity and diabetes. To quote Cha: "Enjoyment of indolent repose or of excessive sleep . . . , (indulgence in) preparations of molasses and other articles that engender phlegm are the causes of *Prameha*". Su is even more outspoken: "An idle man who indulges in day-sleep or follows sedentary pursuits or is in the habit of taking sweet liquids or fat-making food, will ere long fall an easy victim of the disease". Va says: "If food, drink, and activities are such that they favor the formation of fat, urine and phlegm, then as a rule *Prameha* will ensue"; or: "*Madhumeha* derives either from over-nutrition or has its origin in the wind-born disappearance of the *Doshas*".

2.) Diabetes from other causes:—Cha blames as a potential cause of diabetes regular intake of new rice and certain foods like the flesh of animals that have marshes for their habitat. Va enumerates a list of provoking substances, among them "rack and cowmilk".

We may see in such peculiar trains of thought the interpolation of mystical and often irrational material from the *Vedic* scriptures into the later systems of *Ayur Vedic* medicine.

4. *Symptoms and Signs:*—Here we meet the same combination of good and even startling observations on the one hand and either superstitious or faulty beliefs on the other.

a. Symptoms and signs based upon correct observation:–We find in the *Cha Sam* the following differentiation as to constitution of diabetics: strong and corpulent persons are contrasted with lean and weak ones. Both types may become victims of the disease but should be treated differently.

Cha's and Su's reference to the attraction of insects to the sweet urine of diabetics has already been mentioned. According to the Bower Manuscript dogs are attracted to the sweet urine, and lick it.

Thirst, frequent and copious urination, obesity and general lassitude are known to Cha and Su. Among the symptoms of the *Pittaja*-types we find chronic diarrhea and heavy thirst; among those of the *Vataya*-type the longing for food of all tastes. All *Madhumeha* patients are said to "seek a halting place while walking, want a place to sit on while halting, lie down when they find a sitting place, and fall asleep when they lay down."

Knowledge of incapacity of *Prameha* sufferers to have sexual contact is ascribed to Cha and Su alike.

Va stresses the profuse secretion of sweet urine in *Iksumeha* and *Madhumeha*. He also knows of the severe thirst that plagues the persons suffering from *Prameha*, and his inclination to digestive upsets. Wind-born *Prameha* is said by him to be associated with asomnia and emaciation; complicating abscesses with intolerable pain, particularly in obese patients.

b. Symptoms and Signs of a vague and uncharacteristic nature:–These are as numerous as they are diversified; many of them are uncharacteristic and even fantastic. They are enumerated in the textbooks of the three authors more or less identically. It may be sufficient to list them here collectively though roughly arranged according to the systems involved.

1.) Discoloration of urine, dysuria, piercing pain in the testicles, pricking pain in the bladder, shooting pain in the penis;

2.) Excessive perspiration, fetid smell of the body, excessive or incoordinate growth of hair and nails, burning in the palms of the hands and soles, coldness of skin, clotted hair;

3.) Chest pain, dryness of throat and palate, sensation of sweetness in the mouth, bad smelling breath, slimy deposit on the tongue, teeth and palate, expectoration of mucus, palpitation of the heart;

4.) Soreness in the eyes, coating of the tympanum;

5.) Acid eructations, colicky pains in the abdomen, diarrhea or constipation, jaundice;

6.) Love of cold, fever, shivering, frustration;

7.) Harshness of the features;

8.) Fatigue, asomnia.

Facing such a vast collection of heterogenous symptoms and signs we may get rather doubtful as to the clinical acumen of our authors. We should, however, not overlook the following two points: 1. Much of the uncritical folklore deposited in the *Vedic* scriptures crept surreptitiously into the textbooks and attached itself to their contents and even to their style; 2. *Prameha* in its original meaning comprised all sorts of urological diseases to which *Iksumeha* (syn. *Madhumeha*) was added by pardonable error.

5. Complications:—From the preceding list of symptoms and signs we may at least draw the conclusion that old Hindu medicine had already some idea of the different degrees of severity of diabetes, its inclination to going from bad to worse, and its readiness to attack and damage all systems of the body. The *Tridosha*-theory, though crude and imperfect, anticipated the humoral-pathological conceptions of more recent times and asked already for looking at the diseased not as a conglomoration of organs but as an indivisible unit.

a. Acidosis:—We find in recent literature (N. S. Papaspyros, 1952) the supposition that the old Hindu physicians were acquainted with acidosis. This is substantiated by the statement that in Cha's text it is mentioned that, in advanced cases, particularly those complicated with abscesses and carbuncles, excessive thirst, shortness of the asthmatic breath, extreme weakness, sensation of intoxication and even loss of consciousness may appear. Su adds to these symptoms bad smelling breath, somnolence and vomiting. Va mentions nausea, anorexia and mental confusion in addition to the symptoms listed by the two other writers.

b. Abscesses and Carbuncles:—All three authors dedicated whole chapters to the occurrence of abscesses and carbuncles in *Prameha.*

Cha describes seven kinds of "eruptions" which *Prameha* patients may get, foremost through overindulgence in food, faulty nutrition and accompanying laziness. The eruptions *(Pidaka)* are named separately according to their location, appearance and severity. The most dreaded is the species called *Vidradhi* (abscess) which may be either external or deep-seated. The latter is called *Granthi;* it occurs in completely neglected cases, is accompanied by grave symptoms (excessive thirst, dyspnea), is extremely painful and affects the whole body, the central nervous system included. The clinical features of *Vidradhi* depend upon the part of the body affected. If, for instance, the *Granthi* settles in the thorax, the symptoms are excessive pain in the region of the heart, a special form of asthma *(Tamaka),* fainting, loss of consciousness, and finally consumption.

Su knows of ten different types of *Pidaka* occurring in *Prameha.* His description is essentially the same as Cha's.

The Ah of Va enumerates also ten kinds of *Pidaka;* he, too, is most communicative about *Vidradhi.* Its symptoms are said to be different according to the origin of the abscess in wind, phlegm or bile. If it is caused by the simultaneous fault of all three *Doshas,* it is accompanied by all symptoms combined.

6 Treatment:—Care of *Prameha*-patients was of necessity purely empirical. The wealth of endogenous herbs and drugs, their laborious and meticulous preparation and the exact prescriptions concerning their administration are as admirable as they are often confusing and even repellent.

So rich is the Indian flora in medicinal herbs that Cha knew about 500, Su about 700 of them.

a. Cha Samhita:—Cha recommends for the strongly built patient the liberal administration of purgatives and emetics as the first step in treatment. For the lean and weak individual treatment should be started with an attempt to improve the bulk of the body by adequate nutrition. In either case treatment with drugs should begin only after "the fundamental defect" had been corrected. A rich nutritive diet should then be given in all kinds of *Prameha.* No spare diets or fasts are allowed in this stage lest consumption, anuria and other grave symptoms supervene. The diet should mainly consist of dishes made from flour of barley mixed with water (*Manthas*). They are given in addition to a light diet and in connection with certain decoctions and electuaries. Certain varieties of rice may be given instead of barley. The admixture of honey to many of the dietary and pharmaceutical remedies is considered important.

Perhaps such a diet, rich in carbohydrates, was already an anticipation of our modern dietary conceptions. We are also reminded of the so-called "oat-days" (v. Noorden), so often applied in the preinsulin era.

Measured on such relatively sound therapeutic principles it is the more astonishing when we find in the same context the following passage: "Diverse kinds of food made of barley that has passed undigested with the excrements of asses, horses, kine, ducks and porcine should be given to the patient". Only the unsavory memory of the *Dreckapotheke* in the European Middle Ages prevents us from thinking too harshly about such remedies in Old India.

Cha advises the administration of a number of drugs in the form of decoctions. The nature of these drugs differs according to the element which is disturbed and causes the variety of *Prameha* under treatment. For the combination of two damaging elements, e.g. bile and phlegm, special instructions are given: "A person that is affected with *Meha* born of bile and phlegm should lick certain drugs reduced to powder and mixed with honey". Another example is this: "The medicine called *Lodhrasava* promptly destroys all varieties of *Meha* that are born of bile and phlegm".

Even preventive therapy was known to Cha: "One who eats fried barley and the diverse edibles prepared with barley and dried *Caktu* never gets any

kind of *Meha*". He also knew the value of physical therapy: "All kinds of *Meha* may be kept off by diverse kinds of physical exercise, by having one's body strongly rubbed, by baths and washing of the body, and by the use of certain unguents".

"Wines of excellent and well tried taste" are recommended.

In case of complicating abscesses, as far as treatment is possible at all, Cha advises skillful surgical therapy.

b. Susruta Samhita:—Su fortifies the emaciated patient in the same way as Cha does, with nutritious food and drink, and he submits the obese individual to weight reduction, physical exercise and depletory measures. After completion of this preparation, the specific treatment begins and consists of adherence to a rice diet in combination with a number of drug remedies. In contrast to Cha, Su interdicts the intake of wines, liquors and the juice of sugar cane. Cakes and meat are also forbidden. Curiously enough, sweetening with honey in liberal amounts is allowed in the preparation of food as well as of decoctions.

Su makes social distinctions in the treatment of the diabetic clientele. He advises that the prescribed diet and decoctions should be even more liberally sweetened with honey if one deals with a patient who is "either rich or of royal blood or of an uncooperative mind". Such a patient should also "frequently drink liquor prepared from honey, and eat meat roasted on a gridiron over charcoal fire".

If this sounds strangely amusing, the continuation of the text is repulsive: ". . . The powdered dung of a camel, a mule or an ass should be given to such a man in the food"; and: ". . . he should constantly follow the track of cows and take their dung and urine for food and drink". Since Su goes on to say that to the meals given to "such a man" should be added "soups saturated with asa fetida or mustard", one cannot help wondering whether he wants to take revenge on the demanding or rebellious patient.

Su also gives special instructions for the treatment of the Brahman suffering from *Prameha*. "He should live on the grain fallen from plants, study the *Vedas* and draw chariots occupied by other Brahmanas".

The poor individual of low social standing is, from an antidiabetic view, somewhat better off than his rich or royal or priestly fellow-sufferer. Su prescribes for him "to live like an ascetic, feed on alms, do hard work like sinking wells, and walk long distances without shoes and umbrella".

The physical regimen prescribed by Su is as reasonable as that advised by Cha: "Regular exercise, active sports including wrestling and riding on a horse or elephant, long walks, etc.".

For complicating abscesses, Su grades the treatment according to the severity of the case. In mild cases he believes it sufficient to advise fasting peri-

ods, certain decoctions, and the drinking of the urine of a she-goat. He warns such a patient that he will become worse if he goes on "using sweet articles of food". Emetics and purgatives should be administered if the condition progresses. Should these not help either venasection should be performed, various herb remedies given and eventually surgical interventions resorted to "lest the pus eats into the deeper tissues and creates large cavities inside. Hence a case of *Prameha* complicated by *Pitaka* should be remedied at its very outset".

The various drugs and their laborious preparation are described in minute detail and listed by their special names (*Dhanvantara Ghrita, Aragradhadi*, etc.). All of them are praised as very effective in *Prameha*, complicated with abscess. For the patient abandoned as incurable by other physicians, a special remedy, *Silajatu*, is recommended by Su. It contains eight different metals and is supposed to be a panacea in *Madhumea*. Another medicine is called *Tuvaraka-Kalpa;* its use for six days "ensures the cure of every type of diabetes so that the patient would be able to live for a period of 200 years"(!).

c. Vagbhata Samhita (Ah):—Ah follows approximately the same therapeutic lines as Cha and Su. Subsequent to preparation with emetics and purgatives the patient is given one of the many decoctions available in the Indian pharmacopea; the special decoction is chosen according to the condition of the patient and is always mixed with liberal amounts of honey. Food and beverages are made from grain products, particularly barley, rice and wheat. Fatty substances are given only when "wind" is the causing agent of the disease. Legumens and beans are also recommended; so are sauces and delicacies made from *Eugenia Jambolana*, and venison roasted on the spit.

Only a small choice of the manifold and detailed prescriptions, dietary and pharmacological, can be given here. The comprehensive knowledge of officinal plants and herbs, manifested in these prescriptions, makes us blush at our own ignorance.

More reasonable than all these elaborate regimes appears to us the importance attributed by Va to simple ways of life and physical exercise: "Without money, umbrella and shoes, and living like a hermit, the patient should walk long distances or dig ponds or follow the cows on their wanderings about". It does not surprise us that Va also advises such a man "to eat the excrements of the cows and drink their urine while he accompanies them on their wanderings".

There are also detailed prescriptions as to decoctions and ointments for the treatment of complicating abscesses. Mature abscesses should be opened surgically even if they are "internal".

In case of survival, the patient should be painstakingly supervised and treated after a lapse of about 10-12 days with certain foods and with juices made from special herbs.

Va must already have known the truth of the saying that prevention is better than cure: "It is necessary to prevent any inflammation in diabetes with greatest care. For, as soon as inflammation has taken place, its improvement and cure depends upon the will of the Gods".

7 *Prognosis:—a. Charaka Samhita:*—Here the prognosis is believed to be determined by the *Doshas*: "The ten varieties of *Meha* that are born of excited phlegm are curable; the six varieties that are born of excited bile are suppressible; the four that are born of excited wind are incurable".

In regard to the incurable varieties, Cha is of the reprehensible opinion that "there is no need of puzzling the brain about their treatment".

"Incurable" are also called those cases of *Meha,* irrespective of the responsible element, "which linger on with their incubatory symptoms". The same verdict is given to congenital *Prameha.* In cases complicated by abscesses in the vital parts, the physician should be prepared to expect the outcome to be invariably fatal. This is particularly stressed in the case of internal abscesses that appear in the thoracic region, the navel and the anal canal. Cases of diabetes which are caused by disorderly function of all three elements together, must also be considered to be lost.

All other conditions of *Prameha* may become either attenuated or even cured by proper treatment. Cha ends the seventh lesson of his *Sutra Sthana* with the sentence still acceptable to us: "The enemy (i.e. the disease) is always in one's immediate proximity. One endowed with wisdom should, therefore, always observe oneself and conduct oneself with concentrated attention, desiring to have a long life."

b. Susruta Samhita:—Su also maintains that all the ten varieties of *Prameha* caused by deranged phlegm are curable, while in the bile-types only palliation is possible, and most of the wind-born types are incurable. The latter are those in which the way the symptoms are described (excessive thirst, convulsions, etc.) points to acidosis. Cases caused by the simultaneous fault of all the three *Doshas* should be given up as incurable.

As to abscesses appearing in the region of the heart, arms, head, shoulders, back or any of the vital joints of the body, and attended by extreme prostration, Su is of the same sinister opinion as Cha and advises the physician to abandon such patients as incurable. The same advice is given in respect of cases of the wind-type, with or without accompanying abscess.

Su goes so far as to say that "any *Prameha* patient with deep-seated abscess and distressing symptoms should be pronounced as suffering from *Madhumeha* and adjudged incurable". He continues; "All types of *Prameha,* not properly treated or attended to at the outset, may ultimately develop into those of *Madhumeha* types which are incurable".

When in an internal abscess the secretions (pus etc.) take "an upward course", the patient "invariably dies and cure by incision may be attained only occasionally". The internal abscesses seated in the regions named above, end in death even if surgically opened. All cases of abscesses in which the bone marrow is involved and suppurates are fatal as well.

Su brightens this gloomy picture somewhat by giving in full detail the recipes of several decoctions which he recommends as "sovereign medicines in all types of *Prameha*". Among other remedies, a certain oil *(Tuvaraka-Kalpa)* is described which "when taken for five days under favorable astral combinations would ensure the cure of every type of *Kushthameha* and *Madhumeha*".

The following statement of Su seems to be of interest: "Females are less liable to develop severe complications like deep-seated abscesses, as by the monthly discharge their bodies and humors are purified."

c. Vagbhata Samhita (Ah):—Va denotes those patients as incurables whose *Prameha* is caused by bile. Even they may, however, be cured "if the fat is not corrupted too much". But regarding abscesses, Va is as pessimistic as his predecessors: "An abscess should be abandoned as hopeless if it owes its origin to the simultaneous action of the three *Doshas;* if it is located in the regions of the heart, navel or bladder; and if it flows out through the mouth". An emaciated patient who suffers from complications is also designated incurable.

Even in incurable cases Va strikes a hopeful note: "If a diabetic has been abandoned as incurable by his physicians, he should eat a certain amount of bitumen and he will be well again". On reading this particular passage, one cannot help wondering whether it is not an interpolation by some later and more compassionate author.

Comment

First of all it should be stated that the evidence gained by the research of competent scholars justifies the assumption that Indian classical medicine, though old, should not be called ancient. When we place the time of its origin at or around the middle of the first millenium A.D., we become conscious of the fact that this would be roughly 1,000 years after Plato, Pericles and Hippocrates. Even were we to go 500 years further back, the beginnings of *Ayur Vedic* medicine would coincide with Roman culture at its peak. Such considerations will protect us against uncritical acceptance of the often chauvinistic pride of modern Indian writers who claim priority in cultural achievements for their own past, not only in medicine but also in many other fields of science (B. S. Jee, 1927). The mystical and supernatural cloud into which the origin of their medical science has been embedded by the Indians themselves, has its analogy in the fantastic legends that surround their religious systems (cf. the cosmic reverberations at the time of Buddha's death as related in the Holy Scriptures

of Buddhism). Such ornamentation is understandable in matters of religion but not easily acceptable in matters of science. Taking ornamentation and legends for what they are, we do well to place the standard textbooks of *Ayur Vedic* medicine, at least in their present form, into the very early Middle Ages and later. This assumption does not preclude the possibility that much earlier Tantras of Atreya, Dhanvantari, etc., now completely lost, formed the nucleus of the later writings. Their authors probably used the scattered medical knowledge still to be found in the *Vedic Samhitas, Brahmanas, Aranyakas, Upanishads,* etc.

With regard to our particular subject, it is a mixed impression which we gain of the old Indians' knowledge about diabetes mellitus. The disease is ranged by them as a subdivision of a large group of urinary conditions with which it has but an external affinity. The Indian writers of old must themselves have felt this inconsistency, since they tried to make up for it by declaring that every variety of *Prameha,* if not properly taken care of, will end up in *Madhumeha.*

The physiological fundamentals are purely speculative and arbitrary; the therapeutic principles are in part highly debatable and, at their best, crudely empirical.

It should not be passed over lightly that the attraction of insects by sweetness of the urine, pointed out by Cha and Su, and now almost generally accepted as conclusive proof of their familiarity with diabetes, does not seem convincing to all. One expert scholar (Mueller, 1932) stresses the fact, that nowhere in the texts is there any mention of tasting the urine with the tongue. He is, therefore, not willing to accept the bare fact of insects being attracted by the urine as indisputable evidence of the old Indians' capacity to diagnose diabetes. He does not, however, plainly deny this possibility; and with this reservation he is in accordance with the statement made by highest authority, almost 100 years ago, that the old Hindu physicians distinguished themselves by many outstanding qualities, and especially "by the gift of keen and excellent observation" (H. H. Wilson, 1864).

Mueller further points out that the second chief symptom of diabetes, namely the increased output of urine (Polyurea) is not clearly defined in the textbooks and not conclusively differentiated from frequency of urination (Pollakisuria). It seems relevant, however, to recall that among the 20 varieties of *Prameha* there is one named *Hastimeha* (urine of the elephant) which takes its name from the copious amounts of urine secreted by those animals and might very well be the reference to polyurea in diabetes.

The argument has been raised whether the symptoms described in the alleged presence of *Prameha* are sufficiently pathognomonic when we consider their multiplicity and vagueness. In addition, Mueller (1932 b) wonders why

early European physicians, when in touch with their Indian contemporary colleagues, never heard them talk about diabetes. And, finally, he is puzzled by the liberal use of honey and sugar in the treatment of patients afflicted with diabetes.

The first two of these objections do not seem important enough in themselves to shatter our conviction that the old Hindus were in some way, no matter how crude and imperfect, acquainted with diabetes. The third objection can be refuted on the basis of analogy with modern dietetic concepts which ask for relatively large amounts of carbohydrates in the diet of the average diabetic.

The last point to be discussed is the astonishing emphasis put by the Indian authors upon inflammatory complications (such as carbuncles and abscesses), while acidosis and coma seem to have been known to them much less distinctly. The predominance of one out of so many possible complications, and the infaust prognosis attached to it, may be explained, however, by the well known fact that any disease may run a quite different course in different countries or at different periods of time. Syphilis, for instance, is very frequent among the Arabs in the Near East while general paresis and *tabes dorsalis* are practically unknown among them. And, whereas syphilis had a high mortality-rate at the time of the crusades, it gradually lost much of its initial deadliness in the course of the centuries. What is true for infectious diseases may also be applied to diseases of metabolic origin. Incidence and severity of gout in modern days are quite different from what they were in 18th cent.-England. We may, therefore, by analogy, assume that diabetes in old India was probably less prone to acidotic conditions and much more to inflammatory complications.

Notwithstanding all the more or less justifiable objections, the fact remains that the old Hindus were the first to recognize and systematize a disease which comes near to what we nowadays call diabetes mellitus. It is, moreover, highly remarkable that, in contrast to their Greco-Roman contemporaries, they interpreted their observations as the result of metabolic deviations, either inherited or acquired. They were, in addition, well aware of the close etiological relationship between obesity caused by overnutrition and the disease which they called "honey-urine". How little more did we know before Mehring and Minkowski published, in 1889, experimental glycosuria, subsequent to extirpation of the pancreas in animals, and Banting and Best, in 1921, discovered insulin!

We may, therefore, still accept the appreciative conclusion of Sir William Hunter (1718-1783) that "Hindu medicine was an independent development. Arab medicine was founded on translations from Sanskrit and, in turn, European medicine down to the 7th century A.D. was based upon the Latin versions of the Arabian translations."

By accepting this statement we do not assert that Indian medicine knew everything first and the European of old knew nothing. Every culture and every age have their special merits. What we can and should admit is the fact that the old Hindus were the first to know something about human diabetes and certainly knew more about it than their Western successors of much later times.

Summary

Based upon translations of the three most important textbooks of *Ayur Vedic* medicine, an attempt has been made to present and evaluate the knowledge of their authors (Charaka, Susruta, Vagbhata) as to diabetes mellitus. A short outline of the history of old Indian medicine in general seemed indispensable as introduction to the main subject.

The author wishes to express his sincerest thanks to Dr. G. V. Asolkar, College of Science, Nagpur, India, and to Dr. V. W. Karambelkar, Head of the Manuscript Section, University Library, Nagpur, India, who both were of invaluable help in the final revision of this paper.

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President's Message

The Good Neighbor Policy Works

Friendship and good-will is accomplished as easily as you wish to make it. Those of us who attended the National Assembly of Surgeons in Mexico City found our hosts most anxious to serve and please.

Many of us gave scientific papers. Every presentation of a paper from the United States was well attended; with standing room at a premium. This was possible because 80 per cent of the doctors understood English. All papers had been translated into Spanish beforehand and were distributed to each person as he entered the auditorium where the lectures were given.

Our Secretary-General Lynn A. Ferguson gave a breakfast to our members in Mexico. They brought interested guests and we had an attendance of 16. The discussion brought out the need for a formula of initiation fees and yearly dues which would be consistent with our money exchange. In return, there is a need for our Annual Convention in one of our neighboring countries at least every five years.

Remember, any one of us could engender considerable good neighbor good-will for the A. C. G. with a minimum of effort and at the same time receiving great rewards, in personal enjoyment, and satisfaction, while visiting and traveling in Central and South America. We must not miss this opportunity.

Arthur A. Kirchner

NEWS NOTES

College Regional Meeting

A regional meeting of the American College of Gastroenterology will be held in Grand Rapids, Mich. The one-day session will take place on Sunday, 17 March 1957.

Further details concerning the program will be found in the next issue of the journal.

Members of the medical profession are cordially invited to attend.

Annual Meeting Board of Trustees

The Annual Meeting of the Board of Trustees of the American College of Gastroenterology was held on 14 October 1956 at The Roosevelt in New York City.

Dr. Lynn A. Ferguson, Chairman, presided.

Routine communications and administrative matters were disposed of.

The College was advised of the deaths of Drs. Adolf A. Weiss, Israel Mostkowitz, Foster H. Bowman, the Treasurer, Dr. Elihu Katz and a member of the Board of Trustees, Dr. Samuel S. Berger. Letters of condolence were sent by the Secretary.

Dr. James T. Nix, President, reported on the activities of the College during the past year and suggested several matters for the consideration of the Board during the coming year. He thanked the Board, the officers and committee chairmen for their help during the past year.

Dr. Ferguson, in turn, expressed the appreciation of the Board and the officers to Dr. Nix for his able administration.

The Acting Secretary-General, Dr. Ferguson reported on his trip to Europe and the European and Mediterranean Congress of Gastroenterology in London.

Because of the death of the Treasurer, Dr. Elihu Katz, the financial report was prepared and submitted by the Executive Secretary.

The Executive Secretary, Mr. Daniel Weiss, presented a report of the work of his office and advocated the assigning of definite areas of responsibility to the Vice-Presidents and the President-elect.

Committee reports were received from Dr. Frank J. Borrelli, Chairman of the Program and Graduate Education Committees, Dr. Lynn A. Ferguson,

Chairman of Public Relations Committee, Dr. Samuel Weiss, Editor-in-Chief, of THE AMERICAN JOURNAL OF GASTROENTEROLOGY, Dr. H. Necheles, Chairman of the Research Committee, Dr. Edward J. Krol, Chairman of the Finance Committee, Dr. I. R. Jankelson, Chairman of the Constitutional Revision Committee, Dr. Lynn A. Ferguson, Chairman of the Nominating Committee, Dr. Frank J. Borrelli, Chairman of the Credentials Committee and Dr. Louis L. Perkel, Chairman of the Committee on Hospital Relationships.

Dr. Joseph Shaiken, Chairman of the Special Committee on activation of chapters reported for his Committee and submitted recommendations for rules and regulations governing the granting of chapter charters, which were then adopted by the Board.

Dr. Arthur A. Kirchner, Chairman of the Special Committee on Membership, reported on his activities and the goals for future membership drives.

Following the adoption of the requirements for granting charters, the applications for chapter charters for New York and Milwaukee were approved and charter No. 1 was granted to New York with charter No. 2 given to Milwaukee.

The Board voted to revert to the old system of numbering conventions effective with the 1957 convention which would become the 22nd Annual Convention.

The subject of a retirement program for employees of the College was presented and discussed.

Dr. F. H. Voss and Dr. William B. Rawls, whose terms of office on the Board had expired, were thanked for their untiring and devoted efforts on behalf of the College and for their contributions in advancing the work of the organization.

THIRD ANNUAL CONVENTION
AMERICAN COLLEGE OF GASTROENTEROLOGY

The Third Annual Convention of the American College of Gastroenterology was held at The Roosevelt in New York City and was well attended by both members of the College and guests.

The six medical schools in New York City cooperated by each presenting a panel discussion on a phase of gastroenterology and allied subjects. These panel discussions will be published during the year in THE AMERICAN JOURNAL OF GASTROENTEROLOGY. In addition to the panels, there were many individual papers presented which also will be published.

The main speaker at the Convocation Ceremony on Sunday evening, 14 October 1956, was Dr. George E. Armstrong, Vice-President for Medical Affairs

Part of the group which participated in the Annual Convocation of the American College of Gastroenterology at the Roosevelt in New York City, 14 October 1956. Seated in the first row are the officers and guests of the College including: Dr. James T. Nix, President; Dr. Arthur A. Kirchner, President-elect; Dr. C. Wilmer Wirts, Dr. Joseph Shaiken, Dr. Henry Baker, Vice-Presidents; Dr. Lynn A. Ferguson, Chairman, Board of Trustees; Dr. Theodore S. Heineken, Secretary; Dr. Frank J. Borrelli, Chairman of the Convocation; Dr. Asher Winkelstein, recipient of Honorary Fellowship; Dr. George E. Armstrong, guest speaker, Dr. Anthony Bassler, Honorary President; Dr. Samuel Weiss, Editor-in-chief of THE AMERICAN JOURNAL OF GASTROENTEROLOGY and Dr. Edward J. Krol, Marshal.

of New York University and Director, N.Y.U.-Bellevue Medical Center. The invocation was delivered by Rev. John Graham, Church of St. Jean Baptiste and the benediction by Rabbi O. Asher Reichel of the West Side Institutional Synagogue. Dr. Thurman B. Givan, President-elect of the Medical Society of the State of New York and Dr. Samuel Z. Freedman, President-elect of the County of New York welcomed those attending. A photograph of part of the group attending the Convocation appears on the previous page.

Dr. Asher Winkelstein of New York City received an Honorary Fellowship and certificates were presented to the new Fellows of the College.

At the luncheon sponsored by Burton, Parsons Company of Washington, D. C. on Monday, 15 October 1956, the guest speaker was Dr. I. Snapper, Director of Medical Education at the Beth-El Hospital in Brooklyn and Medical Coordinator of the Course in Postgraduate Gastroenterology.

Dr. Arthur A. Kirchner, the incoming President, received the insignia of office from Dr. James T. Nix, the outgoing President at the Annual Banquet of the College on Tuesday evening, 16 October 1956. Dr. Nix was presented with the Past President's key by Dr. Lynn A. Ferguson, Secretary-General, and toastmaster of the evening. The presentations of the 1956 Ames Awards were made to the recipients who were present in person.

Annual Meeting of the American College of Gastroenterology

The Annual Meeting of the American College of Gastroenterology was held at The Roosevelt in New York City on Sunday, 14 October 1956 with Dr. James T. Nix, President of the College presiding.

Dr. Nix presented a report of the activities of the College during his administration and thanked those who worked with him for their cooperation.

A minute of silence was observed for the late Dr. Roy Upham, Secretary-General, Dr. Elihu Katz, Treasurer and Dr. Samuel S. Berger, Trustee, who had died during the year.

The report of the Treasurer was presented by the Executive Secretary who stated that although several of the membership still had not paid their dues for 1956, the number in arrears was the smallest for any previous year.

Dr. Frank J. Borrelli, Chairman of the Credentials Committee, reported that the applications of 17 new Fellows, 23 new Associate Fellows and 12 new Members had been acted upon in the past 12 months. In addition, 15 applications for advancement to Fellowship and 8 for advancement to Associate Fellowship had been recommended to the Board of Trustees which had approved them.

As Chairman of the Program and Graduate Education Committees, Dr. Borrelli lauded the six medical schools in New York who had cooperated with him in presenting panels on the program. He thanked the members of the Committees and those who submitted applications to present papers for their efforts in making the program a success.

Dr. Lynn A. Ferguson, Chairman of the Committee on Public Relations, reported on the publicity for the Convention and Course and the regional meeting held last April. He thanked the Executive Secretary and his staff for the work which they did for his committee.

The Editor, Dr. Samuel Weiss, reported on the increase in subscriptions and advertising as well as in the size of the journal.

He thanked the members of the Editorial Board, Dr. James A. Ferguson, Dr. Milton J. Matzner, Dr. Michael W. Shutkin and Dr. Joseph R. Van Dyne and the members of his Abstract Committee for their excellent work in the past year.

Dr. Weiss presented a check for $1,000 to the College, making a total of $5,000 in surplus funds thus far given to the College. Dr. Weiss stated that an additional check for $1,000 would be turned over before the end of the fiscal year.

In the absence of Dr. H. Necheles, Chairman of the Research Committee, Dr. Henry G. Rudner, Sr. presented the report. Dr. Rudner advised that the winners of the Ames Award Contest for 1956 for the best unpublished paper were Dr. Samuel Katz of Buenos Aires, first prize and Dr. I. N. Marks of Edinburgh, Scotland, second prize.

A prize for the best published paper which appeared in THE AMERICAN JOURNAL OF GASTROENTEROLOGY was given to Dr. George B. Jerzy Glass and Marilyn Rich.

The voluntary contribution of $10.00 for the Research Fund is again to be added to the bill for annual dues and it is hoped that enough funds will be made available to establish a Research Fellowship in Gastroenterology.

Dr. Edward J. Krol, Chairman of the Committee on Finance and Budget, presented an estimated budget for 1956-1957, which had been approved by the Board of Trustees. He further advised that the dues and initial fees would be continued at the 1956 rate.

Dr. I. R. Jankelson, Chairman of the Committee on Revision of the Constitution and By-laws, told the meeting that his committee had worked by mail and had prepared and presented several amendments to the Constitution and By-laws which were to be acted upon at the meeting.

Dr. Lynn A. Ferguson, Chairman of the Nominating Committee, presented his committee's report.

The Chairman of the Special Committee on Membership, Dr. Arthur A. Kirchner, reported on his activities to obtain increased membership. He stated that the College now had 825 members consisting of 27 Honorary Fellows; 30 Life Fellows; 315 Fellows; 163 Associate Fellows and 290 Members. During the past year there had been 8 deaths, 4 resignations and 28 had been dropped for non-payment of dues.

Under new business, amendments to the Constitution and By-laws were adopted after careful consideration and discussion.

Governorships for the state of West Virginia and the countries of Cuba, Mexico, Uruguay and Venezuela were voted.

The Secretary reported that no additional nominations for office had been received and upon motion duly made, seconded and unanimously carried, he was instructed to cast one vote for the election of the slate of nominees presented by the Nominating Committee.

Annual Meeting of the Board of Governors

The Annual Meeting of the Board of Governors of the American College of Gastroenterology was held at The Roosevelt in New York City on Tuesday, 16 October 1956.

Dr. Louis Ochs, Jr., Chairman of the Board, presided and 16 of the 19 Governors were present.

Dr. Henry G. Rudner, Sr. of Memphis, Tenn. was elected Chairman to succeed Dr. Ochs who had been elected to the 4th Vice-Presidency of the College.

Dr. Robert T. McCarty of Wisconsin was unanimously nominated to serve on the Credentials Committee for a three year term and Dr. T. Neill Barnett of Virginia and Dr. Harry Barowsky of New York were recommended to the President for appointment to the Nominating Committee.

Dr. Arthur A. Kirchner, incoming President of the College, spoke briefly on the aims and purposes of the Membership Committee as well as other projects which are being considered for the coming year. These were discussed.

The selection of a site for a regional meeting for 1957 was left to the Board of Trustees.

Special Meeting of the Board of Trustees

A Special Meeting of the Board of Trustees of the American College of Gastroenterology was held at The Roosevelt in New York City on Wednesday, 17 October 1956.

Dr. Lynn A. Ferguson, Chairman of the Board, presided. He thanked the Board for their cooperation and expressed his gratitude to them for having been permitted to serve in that capacity.

Dr. James T. Nix was elected as the new Chairman of the Board and he assumed the chair.

Committees, to serve during the year, were appointed upon recommendation of the President, Dr. Arthur A. Kirchner.

Dr. Robert R. Bartunek of Cleveland, Ohio was appointed Trustee to replace the late Dr. Samuel S. Berger.

Dr. Kirchner advised that he had appointed Dr. Samuel W. Yabroff of San Francisco, Calif. to be Governor for Northern California and Dr. Irving A. Levin of New Orleans, La. as Governor for Louisiana. He also appointed Dr. Stanley S. Sidenberg of Cleveland, Ohio to succeed Dr. Bartunek as Governor for Ohio.

Dr. Lynn A. Ferguson was unanimously appointed Secretary-General as was Dr. William C. Jacobson, the new Treasurer.

With the appointment of Dr. Jacobson as Treasurer, another vacancy was created on the Board of Trustees and Dr. Harry Barowsky of New York City was appointed to this position for one year.

Dr. Samuel Weiss was reappointed Editor-in-Chief of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

In addition to the officers specified in the Constitution, Dr. Henry Baker, Dr. Frank J. Borrelli, Dr. John M. McMahon, Dr. Joseph Shaiken and Dr. Samuel Weiss, were elected to serve on the Executive Committee.

The Chairman of the Board of Governors, Dr. Henry G. Rudner, Sr., presented a report of the meeting of the Board of Governors.

To further implement the work of the Board of Trustees and the Board of Governors, a liaison committee consisting of two members of the Board of Trustees, two members of the Board of Governors and two Fellows of the College at large, are to be appointed.

Applications for affiliation with the American College of Gastroenterology from Drs. Lester A. Barnett, Asbury Park, N. J.; Carroll J. Bellis, Long Beach, Calif.; John M. Fernald, Los Angeles, Calif.; Dante A. Gazzaniga, Los Angeles, Calif.; Charles J. Miangolarra, New Orleans, La.; Donald E. Ross, Los Angeles, Calif.; Morton Schwartz, Far Rockaway, N. Y.; Carlo J. Tripoli, New Orleans, La.; David Fishman, Cleveland, Ohio; Harry J. Kanin, Milwaukee, Wisc.; Herbert F. Gaines, Birmingham, Ala.; Pracha Piseshurarit, Philadelphia, Pa.; Robert L. Blackmun, Los Angeles, Calif.; Brewster C. Breeden, Glen Ridge,

N. J.; Leon O. Desimone, Los Angeles, Calif.; Marcel M. Thau, Hartford, Conn.; Sidney D. Thomason, Pomona, Calif.; Richard H. Watt, Beverly Hills, Calif.; Raymond E. Moffitt, Providence, R. I. and Harold L. Schlotthauer, Tehachapi, Calif., were presented by the Credentials Committee and were accepted.

Dr. Franz J. Lust was elected to Life Fellowship and upon having presented the necessary qualifications Drs. Alvin D. Yasuna, Bronx, N. Y.; Erwin H. W. Kersten, Anaheim, Calif.; Cecil Mantell, Staten Island, N. Y.; Paul Metz, Portland, Oreg.; William Offenkrantz, Brooklyn, N. Y. and Louis A. Perrotta, Bronx, N. Y., were advanced.

Drs. Jose Oviedo Bustos, Rosario, Arg. and Frank P. Tocci, Montclair, N. J., were reinstated.

It was voted to hold the 1957 regional meeting in Grand Rapids, Mich. and Chicago was tentatively selected for the 1961 convention.

The establishment of an Emeritus Club consisting of Past Presidents, without the power to vote or to make policy, was established. Its functions will be to assist the Secretary-General and to perform such other tasks as it may be called upon.

New Governor for Lower New York

Dr. Arthur A. Kirchner, President of the American College of Gastroenterology, announced that he has appointed Dr. Joseph Roger Van Dyne of Forest Hills, N. Y. to be Governor for Lower New York, succeeding Dr. Harry Barowsky who was elected to the Board of Trustees of the College.

Dr. Van Dyne is a member of the Editorial Board of The American Journal of Gastroenterology and Secretary of the New York Academy of Gastroenterology, the New York Chapter of the College.

American Academy of General Practice

The Ninth Annual American Academy of General Practice Scientific Assembly will be held 25-28 March 1957, in Kiel Auditorium, St. Louis, Mo.

During the four-day scientific meeting, the doctors will hear outstanding speakers discuss important subjects including infertility, polio vaccination, and the "neglected" pediatric areas, the eyes, ears, and feet. They will visit 60 scientific and 260 technical exhibits.

Dr. I. S. Ravdin, professor of surgery at the University of Pennsylvania, will moderate a panel discussion of pre- and postoperative care. Dr. Philip Thorek, associate professor of surgery at the University of Illinois and professor of surgery at Cook County Graduate School will discuss "Intestinal Obstruction". Three other surgeons will highlight advances in vascular, thoracic, and

neurosurgery. One afternoon will be devoted to a review of procedures that assure birth of "healthy babies" from "well mothers".

Wednesday evening, 27 March, following induction ceremonies for Academy President-elect Malcom E. Phelps, El Reno, Oklahoma, more than 3,000 guests will attend a President's reception and dance honoring J. S. DeTar, M.D., Milan, Mich., president of the Academy.

In Memoriam

We record with profound sorrow the passing of Dr. LeRoy P. Duggan of Houston, Texas, Fellow; Dr. G. Irving Levine of Jersey City, N. J., Associate Fellow; Dr. Virgil G. Presson of Tucson, Ariz., Associate Fellow and Dr. William Stahl, Sr. of Danbury, Conn., Associate Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved families.

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ESOPHAGUS

THE ETIOLOGY AND TREATMENT OF PEPTIC ESOPHAGITIS: Frederick S. Cross and Earle B. Kay. Ann. Surg. 143:360-368 (March), 1956.

After a review of the pertinent literature and general discussion of esophagitis, the authors present 55 cases seen between January 1, 1949 and January 1, 1955.

Conservative treatment as definitive therapy is recommended in patients falling into the following categories: 1. Acute esophagitis of minimal or moderate degree, such as produced by severe vomiting. 2. Chronic esophagitis not associated with a demonstrable hiatal hernia. 3. Esophagitis with hiatal hernia in patients in whom elective surgery may be otherwise contraindicated, so long as the symptoms can be adequately controlled conservatively.

The medical regimen for those cases is simple and consists of an ulcer-type diet, antacids, and elevation of the head of the bed.

The indications for surgical treatment in esophagitis are the same as those for peptic ulceration, persistence of symptoms in the face of an adequate therapy, significant bleeding, perforation, and stenosis. If a hiatal hernia is associated with the esophagitis, the indications for operation are liberalized, since complete control of the symptoms and progress of the disease can be expected following the repair of the hernia.

PAUL MATLIN

INTESTINES

A COLOSTOMY IRRIGATOR OF IMPROVED DESIGN: Eugene H. Weissenberg and H. M. Thompson. J.A.M.A., 159:1201, (19 Nov.), 1955.

The authors describe an ingenious colostomy irrigator which they have devised for the purpose of making irrigation less unpleasant with less clean-up afterwards and accomplished with a minimum of inconvenience.

W. K. BILLINGSLEY, JR.

PRACTICAL ASPECTS OF INTESTINAL OBSTRUCTION: W. Edward French. Clin. Med., 2:1087, (Nov.), 1955.

From a practical standpoint, all cases of intestinal obstruction are either simple or strangulated. The outcome of simple obstruction is usually good; whereas, the mortality rate of strangulated intestinal obstruction is high.

Simple intestinal obstruction and strangulating obstruction are not always easy to differentiate, but usually can be done. The most important diagnostic, as well as prognostic point, is the response of the patient to proper and adequate preoperative preparation. Fluids and electrolytes should be returned to as near normal, prior to surgery, as time will permit, along with the control of the further loss of these substances. The exact amount of fluids and electrolytes needed to return the patient to normal can be determined very accurately. If good laboratory facilities are not available, one can roughly, and quite frequently correctly determine the needs by simply determining how much the patient has failed to receive over a given period. The daily requirement of each substance multiplied by the number of days the patient failed to receive it will give a rough estimate of how much is needed.

The time of surgery is important. Few conditions require more immediate surgery than intestinal obstruction with a coexistent embarrassment of blood supply. The type of surgery in intestinal obstruction will depend upon the cause of obstruction. After relief of the obstruction, no additional procedures should be done.

JOHN E. Cox

ULCERATIVE COLITIS: J. Ogle Warfield, Jr. Clin. Med., 2:1111, (Nov.), 1955.

The article deals with the pathology, etiology, diagnosis, complications, and treatment of ulcerative colitis. The author stresses the need of continued interest and support of the family physician instead of the specialist whom the patient may consult in his search for some miraculous specific relief. He mentions the complications which may develop in persons who have had ulcerative colitis over a period of years, the intensity increasing with the duration of the disease. The development of cancer in several areas of the large bowel almost simultaneously is to be considered and it is noted the signal symptoms of cancer may be confused with the symptoms of ulcerative colitis in these cases. The author is of the opinion that surgical treatment offers a definite termination of the symptoms and a chance for rehabilitation. He estimates a surgical mortality of four to five per cent, and maintains the accepted permanent, end-type, aversion ileostomy, and a complete colectomy.

JOHN E. Cox

MULTIPLE POLYPOSIS OF THE COLON, OSTEOMATOSIS AND SOFT-TISSUE TUMORS: Robert S. Weiner and Philip Cooper. New England J. Med., 253:795, (10 Nov.), 1955.

Multiple polyposis of the colon is a rare familial disease, but combined with osteomatosis and soft tissue tumor is even more rare. The authors quote only one case report in the literature, adding their own as the second. Gardner et al is quoted with a report of 6 cases in a family group of 51 living people with multiple polyposis, osteomas and three types of cutaneous or subcutaneous lesions (epidermoid cysts, fibromas and poorly defined masses of connective tissue). The lesions were of widespread distribution. Eight other members of the family then deceased were reported to have died of cancer of the colon or rectum all having had multiple cutaneous or subcutaneous lesions and six of these had osteomata. Their conclusion was that a single gene with a dominant mode of inheritance was the most likely explanation for the presence of all the abnormalities in the family group studied.

Dr. Weiner and Dr. Cooper have studied a family group consisting of 4 brothers with multiple polyposis of the colon in combination with osteomatosis and multiple soft tissue tumors. All 4 had been subjected to ileostomy with total colectomy In 3, the resected specimen revealed adenocarcinoma in addition to the multiple

polyps. In 3, soft tissue tumors and osteomata were found. In one, only osteoma of the skull was found, but no soft tissue tumors on physical examination. It is predicated that the probable latent tendency to soft tissue tumor formation did not become evident as yet because of his early death.

A. J. BRENNER

DIAGNOSIS OF CARCINOMA OF COLON AND RECTUM: M. Tischer Hoerner. Ohio M. J., 51:1098, (Nov.), 1955.

Diagnosis of carcinoma of the colon and rectum is at best difficult, as the early symptoms present bizarre patterns.

The right colon, which develops from the midgut, does not show obstruction because lesions do not circle the bowel, but perforate and produce abscesses; the left colon which develops from the hindgut, shows obstruction because of the signet-ring encirclement.

The lesions of the intestinal tract are: 1. adenocarcinoma, 2. scirrhus carcinoma, usually in left colon, and 3. mucoid-carcinoma.

Pain in right colon disease occurs late and is referred to the epigastrium, cramp-like in character, with alternating diarrhea and constipation, but not showing gross blood in the stool.

Transverse colon neoplasm shows pain of an intermittent type, usually mild and related to meals, lessened by passage of gas or by a stool, but characterized by increasing constipation and gross blood in stool, and ultimately partial obstruction.

The lesions of the lower bowel often show obstruction as the initial symptom, but usually present irregularity of stool, abdominal cramping, urgency, diarrhea with blood in stools then obstruction.

Carcinoma of the rectosigmoid and rectum usually produces no pain, but shows change in bowel habit, bloody stools and often in low lesions, rectal tensemus.

All intestinal carcinomas produce increasing anemia.

J. EDWARD BROWN

THE ACUTE ABDOMEN IN THE AGED: A. Standeven. Brit. M. J., 4949:1184, (12 Nov.), 1955.

The author reviews 120 cases of acute surgical abdomen, excluding acute urinary retention, in patients over 70 years of age.

Intestinal obstruction was the most common emergency and carried with it a heavy mortality. There were six cases of strangulated femoral hernia. Most of these were of the Richter's type and may be felt with difficulty in the obese groin. Vomiting in intestinal obstruction especially in the Richter's type of hernia and closed loop obstruction of colon may not be marked in the aged. The passage of flatus or the absence thereof, is of greater significance than the history of the last bowel movement.

Peritonitis is much more frequent than abscess formation in perforated appendicitis.

There were eight cases of sigmoid perforation in which no evidence of carcinoma was found, the etiology being either a perforated diverticulum or a stercoral ulcer. Seven of these cases died.

The problem of diagnosis in the aged is primarily due to the widespread clinical findings which obscure the early localizing signs. Elderly patients are often tougher than they look and can usually withstand operation well, provided it is not delayed too long and is quickly performed with a minimum of trauma. If in doubt it is safer to operate than to observe. Age in itself has no effect on the mortality rate.

ALEXANDER ZABIN

RECURRENT INTUSSUSCEPTION ASSOCIATED WITH HYPERTROPHY OF PEYER'S PATCHES: Ernest L. Sarason, John T. Prior and Ralph L. Prowda. New England J. Med., 253:905, (24 Nov.), 1955.

The authors describe the clinical and pathological findings in a child who underwent five surgical reductions of a recurrent ileocolic intussusception followed by

ileocecal resection with complete recovery. The pathological diagnosis following resection of the terminal ileum and cecum was giant-follicle hypertrophy of Peyer's patches.

Anatomic studies have revealed that during the first year of life the terminal ileum is studded with lymphoid tissue which gradually disappears as the child grows older. A possible explanation of the phenomenon herein described is an inflammatory swelling of the lymphoid tissue resulting in a polypoid mass which is capable of initiating the intussusception. The cause of the inflammation is unknown. It has been observed that the age incidence of intussusception varies directly with the prominence of the lymphoid tissue in the terminal ileum. The authors discuss the relationship of this entity to the norma' lymphatic architecture and to the systemic lymphomatous diseases.

In conclusion the authors state that ileocecal resection appears to be warranted if an ileocolic intussusception recurs more than once even though no tumor can be palpated within the terminal ileum.

CHESTER S. SVIGALS

STEATORRHEA FOLLOWING OPERATIONS ON THE GASTROINTESTINAL TRACT: Douglas G. Cameron, E. H. Bensley, A. English and Phyllis Wood. Canad. M. A. J., 73:819, (15 Nov.), 1955.

Postoperative steatorrhea is not a rarity but cases are being reported with increasing frequency. The etiological factors concerned in this incidence are still obscure.

The syndrome finds symptomatic expression in varied symptom-complexes. Most frequently encountered are: loss of weight, megaloblastic anemia, iron deficiency, osseus discomfort, glossitis, hypocalcemia with osteomalacia and prothrombin deficiency, and clubbed fingers and toes. Diarrhea is not a constant finding. Idiopathic steatorrhea exhibits similar manifestations.

REGINALD B. WEILER

LIVER AND BILIARY TRACT

RESECTION OF A CAVERNOUS HEMANGIOMA OF THE LIVER: L. Gonzalez Cigarroa and M. E. Malakoff. Texas J. Med. 51:768 (Nov.), 1955.

The authors cite a single case report, without discussion or comment, of the successful resection of a hepatic tumor which on microscopic section proved to be a benign giant cavernous hemangioma of the right lobe. The preoperative diagnosis was multiple leiomyomata of the uterus with one large pedunculated leimyoma occupying the right hypochondrium. The patient did well postoperatively without any complications or apparent sequellae.

CHESTER S. SVIGALS

JAUNDICE IN RELATION TO CHLORPROMAZINE THERAPY: Bernard Isaacs, J. G. Macarthur and Rhoda M. Taylor. Brit. M. J. 4948:1122 (5 Nov.), 1955.

The pathogenesis of jaundice with the use of chlorpromazine has not been clarified despite the numerous reports in the literature—including this one.

Of 26 patients treated with chlorpromazine the authors found 3 that developed jaundice. This high incidence was at variance with the over-all 1 per cent reported from psychiatric hospitals in England where doses used were quite high.

The authors try to explain their almost 20 per cent incidence of jaundice to the probable associated liver disease of their treated patients or else to the "sensitization" of the liver by other drugs. From their small series they concluded that it would be wise to avoid chlorpromazine therapy if 1. infectious hepatitis is endemic 2. in the presence of liver disease 3. in malnourished patients 4. when other potentially hepatotoxic agents have been used and 5. when estrogens in particular have been used.

The article again emphasizes the fact that jaundice and possibly even liver necrosis can occur unpredictably with chlorpromazine therapy, small or large doses notwithstanding. In contrast the generally

low incidence of jaundice, which in most cases is self-limited deserves equal comment.

Whether more than one mechanism for jaundice with chlorpromazine exists remains unanswered. The whole subject needs more critical evaluation.

A. M. SUSSINO

ACUTE FATTY METAMORPHOSIS OF THE LIVER ASSOCIATED WITH PREGNANCY. A Distinctive lesion. W. B. Over and T. M. Lecompte. Am. J. Med. 19:743-757 (Nov.), 1955.

The authors present three fatal cases of jaundice occurring at the end of the last trimester of pregnancy. Clinically, the course of these patients was indistinguishable from that of fulminant epidemic (viral) hepatitis. Pathologically, the lesion was found to be readily distinguishable and consisted of extensive fatty metamorphosis of liver cells occupying the central two-thirds of the liver lobule. There was no significant infiltration of inflammatory cells nor was there evidence of necrosis of liver cells. Chemical analysis of the formalin-fixed liver in one of the cases showed that the increased lipid lies almost entirely in the fatty acid moiety. Fatty metamorphosis was also present in the renal tubular epitheleum in all three cases. The literature relevant to this lesion is reviewed. This brings the total cases in the literature to 14, only one of which has recovered. However, the authors feel that the lesion is presumably reversable. They also discuss the effect of pregnancy on liver function and its presumptive role in the genesis of this type of lesion. Both clinical and experimental methods of protecting the liver from fatty changes are mentioned and possible therapeutic measures including high protein intake as well as parenteral fluids and vitamins are discussed. Because of the high fetal and maternal mortality, it is felt that interruption of pregnancy might be in the best interest of mother and child. Needle biopsy of the liver seems to be the only accurate present method of antemortem diagnosis.

JOHN M. MCMAHON

TRANSIENT HEPATIC COMA, I. Clinical Study: J. P. Benhamou and R. Fauvert. La Presse Med. (29 Oct.), 1955.

The authors recall that several publications, prior to the present article, were concerned with a number of cases where hepatic coma had run a regressive course and this even spontaneously. On the occasion of 4 personal typical cases, here reported in detail, they were prompted to review the literature on the subject.

They discuss what should be understood by the term "transient" applied to hepatic coma and what are the diseased conditions in which this transient form of coma may be encountered.

Then they describe the symptomatology as possibly developing within two periods: the precomatose period and the comatose period.

The former was given various names such as "transient hepatargy" or "impending coma" (this being the most used in the anglo-saxon literature).

The precomatose period is characterized by three orders of symptoms and signs which in general appear successively in their evolution as being neurologic, comportment, conscience disturbances. Precoma may not be followed by the condition of real coma.

The comatose period, properly called coma, usually succeeds to the former period in a gradual manner, but may exceptionally appear from the very onset. It is marked by deep sleep similar to physiological sleep, by muscular rigidity, increased osteotendinous reflexes, more rarely convulsive attacks, and particularly by a typical offensive breath (*foeter hepaticus* of the anglo-saxon authors).

After describing the general evolution of this coma, the authors call attention to the diagnostic value of the electroencephalographic changes; by their personal observations were quite conformative of those from the anglo-saxon authors.

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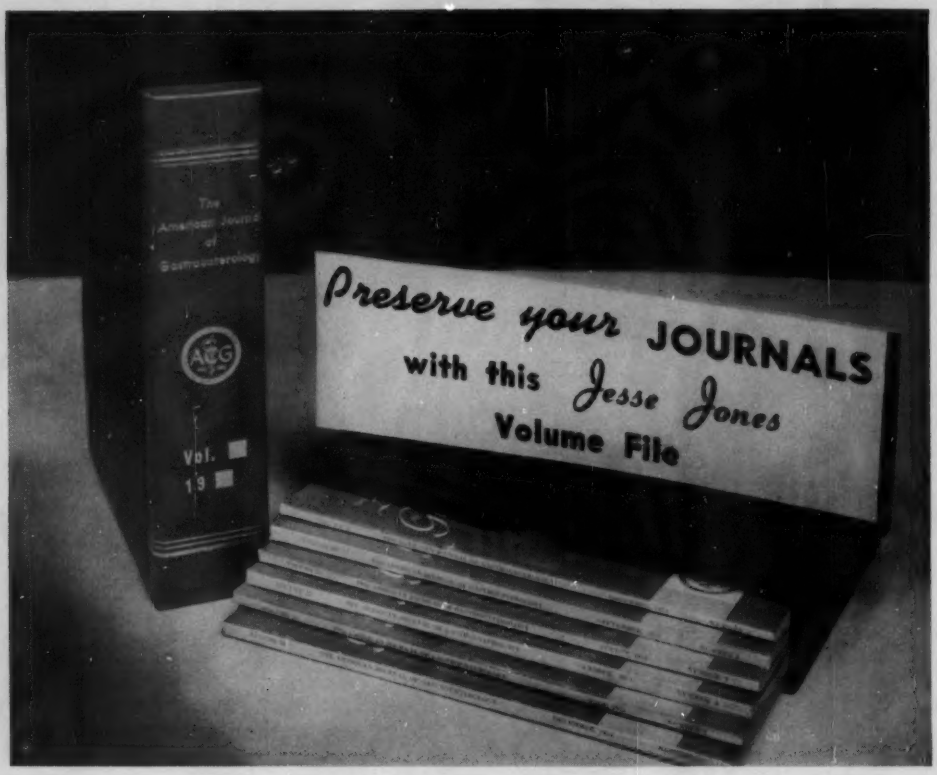

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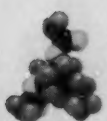

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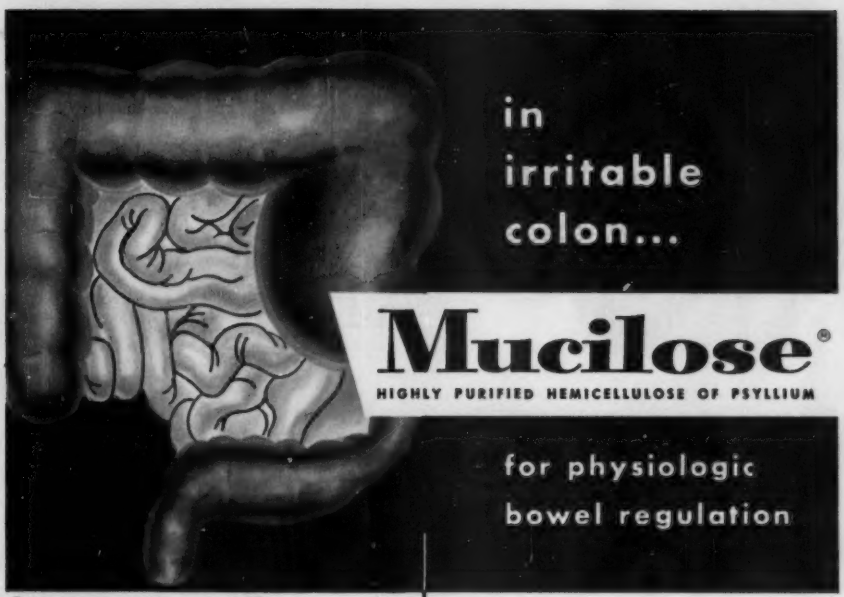

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Winthrop LABORATORIES
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Mucilose, trademark reg. U. S. Pat. Off.

"...the important problem of constipation" in irritable colon should not be overlooked.

"It is imperative that the patient stop taking laxatives."

"The routine use of a hydrophilic colloid such as...Mucilose...is often gratifying, and never contraindicated in irritable colon syndrome even with diarrhea."[1]

MUCILOSE produces bland peristalsis-stimulating bulk resulting in soft, demulcent stools. This is due to its tremendous water-binding capacity (50 times its own weight[2]). Conversely, when taken with small amounts of water, Mucilose restores the normal water balance in the diarrheal phase of colitis by binding loose stool and reestablishing normal fecal colloid.

1. Straughn, R. A.: *Jackson Clin. Bull.*, 13:83, Aug., 1951.
2. Gray, Horace, and Tainter, M. L.: *Am. Jour. Digest. Dis.*, 8:130, Apr., 1941.

MUCILOSE *For Physiologic Bowel Regulation*

not as simple as "APC"...

The search for an analgesic preparation superior to APC has culminated in the development of FALGOS TABLETS. After extensive pharmacological research, alkaline substances – which speed absorption[1] and minimize the side effects of acetylsalicylic acid[2] – have at last been successfully combined with APC in a stable, pharmaceutically elegant tablet.

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In another series of studies in which buffered and unbuffered APC tablets were compared, the buffered material was shown to be definitely superior to the unbuffered tablets from the standpoint of faster, more effective pain relief and better gastric tolerance.

Each Falgos Tablet contains: aspirin 3 gr; acetophenetidin 2 gr; caffeine ⅓ gr; and a balanced proportion of aluminum and magnesium hydroxide.

Indications: Pain of headaches, neuralgias, neuritis, muscular aches and pains, discomfort of the common cold; minor aches and pains of rheumatism and arthritis; before and after dental procedures and tooth extractions.

Dosage: 1 or 2 tablets with water, repeated every three hours if necessary.

Supplied: Bottles of 15 and 40 tablets.

FALGOS®

ANALGESIC-ANTACID TABLETS

1. Lolli, G., and Smith, R.: New England J. Med. 235:80 (July 18) 1946.
2. Schnedorf, J. G.; Bradley, W. B., and Ivy, A. C.: Am. J. Digest. Dis. 3:239 (June) 1936.
3. In press.

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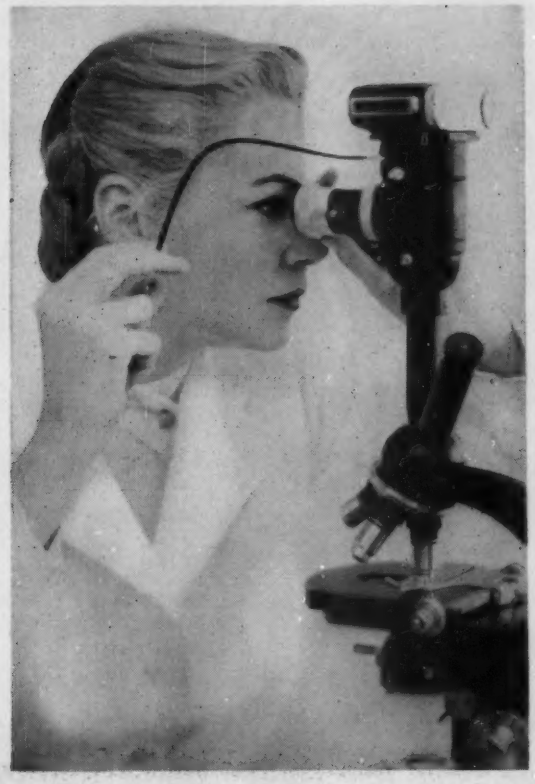

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1. Dolkhart, R. E., Dentler, M. & Barrow, L. L., Ill. M. J. 90:286, 1946.
2. Adler, H. F., Atkinson, A. J., & Ivy, A. C., Am. J. Digest. Dis., 8:197, 1941.
3. Wozasek, D., & Steigman, F., Am. J. Digest. Dis., 9:423, 1942.
4. Williams, R. D., & Olmsted, W. H., Ann. Int. Med., 10:717, 1936.
5. Lieberthal, M. M., Conn. State M. J., 19:86, 1955.

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